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A FRACTIONAL BROMSULFALEIN TEST TO DETERMINE LIVER DAMAGE IN THE NONJAUNDICED PATIENT*

EMMANUEL DEUTSCH, M.D.†

BOSTON

DESPITE the large amount of work that has been done on the functions of the liver during attacks of jaundice, very little attention has been paid to the problem of residual liver damage after the patient has recovered. This is probably because the available methods have failed to show variations from normal in the majority of cases. During the last three years, 50 patients with disease of the liver have been studied in an effort to appraise the amount of residual liver damage, during and after convalescence, by frequent hippuric acid excretion, urinary urobilinogen, icteric index, total, free and ester cholesterol and lipid phosphorus determinations[1] and modifications of the bromsulfalein-excretion test.

Bromsulfalein has been in use for the last fifteen years and is generally considered the most satisfactory dye for determining liver function. Mills and Dragstedt[2] found that the mode of excretion of intravenously injected bromsulfalein is through the reticuloendothelial system, since blocking of these cells with India ink results in marked retention of the dye in the blood stream. Obstruction of the bile ducts does not impair the removal of bromsulfalein to the extent that it impairs bilirubin excretion.[2]

These authors have observed that removal of the dye in dogs appears to occur in two phases.[2] In the first five minutes after injection, 85 to 95 per cent of the dye is removed from the blood stream. A secondary or subsequent phase of varying length occurs after this five-minute interval, during which the remainder of the dye is excreted.

METHODS AND MATERIAL

The hippuric acid excretion was determined by the method of Quick.[3] Normal human beings excrete 2.5 to 3.0 gm. within four hours of the administration of 6.0 gm. of sodium benzoate. Urobilinogen in the urine was determined by the procedures of Watson[4] and Wallace and Diamond.[5] Normal persons excrete up to 4 mg. in twenty-four hours by the Watson method and show urobilinogen present in a 1:16 dilution by that of Wallace and Diamond.

Using the Rosenthal[6] technic, 2 mg. of bromsulfalein per kilogram of body weight was injected intravenously. A control blood specimen was taken just before the injection. One-half hour later, a specimen was obtained, rendered alkaline and compared with color standards.‡ Since it soon became apparent that patients only recently recovered from severe attacks of jaundice showed no retention of the dye after thirty minutes, a modification of technic was tried. Bromsulfalein levels in the plasma were observed at intervals of two, five and fifteen minutes. The two-minute sample showed such high levels in normal subjects that it was discontinued. In 10 normal patients at the end of five minutes, bromsulfalein retention was never in excess of 60 per cent, and the fifteen-minute sample rarely showed more than 5 per cent retention of the dye.

Other investigators have demonstrated the value of the fractional bromsulfalein test, although it has never come into common use. Rosenthal and Bourne,[7] using a fractional bromsulfalein test and the Wallace and Diamond[5] method for urobilinogen in urine on patients following various types of anesthesia, showed that a disturbance in function could be demonstrated with the bromsulfalein test long after pigment metabolism had returned to normal.

MacDonald[8] described a fractional bromsulfalein test using 2 and 5 mg. of dye per kilogram of body weight and taking blood specimens every

*From the Surgical Research Laboratory, Boston City Hospital.

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†Instructor, Courses for Graduates, Harvard Medical School; fellow in surgical research, Boston City Hospital.

‡Prepared by Hynson, Westcott and Dunning, Baltimore.

TABLE 1. *Summary of Data.*

CASE NO.	DATE	BROMSULFALEIN RETENTION 2 MIN. %	5 MIN. %	15 MIN. %	ICTERIC INDEX	HIPPURIC ACID EXCRETION gm.	UROBILINOGEN* EXCRETION mg./24 hr.	ADDITIONAL DIAGNOSIS	RESULT
Acute Infectious Hepatitis									
1		10	5	3	7	4.1			Recovery
2		15	5	2	5	2.8			Recovery
3		25	15	0	7	3.7			Recovery
4	1/31/40		95	5	7		Trace	Glomerulonephritis	
	3/11/40		70	2	6		Trace		Recovery
5	2/8/40		42	3	6	4.0		Pancreatic abscess	
	2/24/40		18	2	6	4.2			Recovery
6			100	20	8		Trace		Recovery
7	5/4/40		100	80	30	1.1	Trace		
	5/16/40		80	35	10	1.7		Healing subacute yellow atrophy	
	5/29/40		80	50	7				Illness continues
	6/20/40		100	10	6	2.8			
	8/1/40		85	20	7	1.4			
	10/26/40		100	90	12	1.2			
8			80	30	5	1.0		Circulation time, 16 sec.	Death of acute yellow atrophy
9			50	2	20	2.8			Recovery
10	9/3/40		100	55	25	2.7		Spontaneous abortion during height of jaundice	Illness continues
	10/24/40		65	40	8	1.7			Re-entry for pyelitis
Acute Toxic Hepatitis									
11	2/27/39	60	20	0	10	3.7		Arsphenamine poisoning	Recovery
	4/22/39	3	0	0	8				
12		8	5	2	7	2.7		Sulfanilamide poisoning	Recovery
13		30	10	2	7	3.7		Carbon tetrachloride poisoning	Recovery
14			10	0	6	3.3		Arsphenamine poisoning	Recovery
15		10	5	3	8	4.1		Arsphenamine poisoning	Recovery
16	8/22/40		100	60	25			Carbon tetrachloride poisoning	
	8/27/40		90	25	10	3.0			Recovery
Chronic Cirrhosis									
17		5	3	0	6	2.9		Portal cirrhosis	Recovery†
18		9	4	2	8	2.5		Portal cirrhosis	Recovery
19		60	3	0	5	2.8		Portal cirrhosis	Recovery
20		60	40	40	7	1.6		Hemochromatosis	Death
21		30	15	2	7	3.8		Portal cirrhosis	Recovery
22		40	30	15	8	1.0	5.7	Portal cirrhosis	Death
23			5	2	8	3.4	0.2	Portal cirrhosis	Recovery
24			45	2	8	2.8		Portal cirrhosis	Recovery
25	1/1/39	100	100	80	8	1.1	0.8	Banti's syndrome	Illness continues
	5/13/40		100	90	15	2.1			
	7/13/40		75	25	30	0.7			Splenectomy
	8/1/40		50	40	12	Vomited			Re-entry
	9/6/40		100	100	15	1.2			
26	1/10/40		100	20	8			Portal cirrhosis, pancreatitis	
	1/18/40		42	2	7				Recovery
	1/31/40		35	2	5	3.9			
27			70	35	6		Trace	Portal cirrhosis, pellagra	Recovery
28	3/25/40		100	20	7		45.9	Toxic cirrhosis	
	4/11/40		25	5	7		3.7		
	5/1/40		100	70	10		18.9		Death
29			60	50	8		60.9	Portal cirrhosis	Death
30			70	40	8	2.5		Essential lipemia	Recovery
31			55	2	8	2.7		Beriberi heart disease	Recovery
32	5/22/40		35	30	6	0.8	15.0	Primary hepatoma	
	7/25/40		45	20	6	2.1		Portal cirrhosis	Death
33			60	30	6	2.2		Portal cirrhosis	Recovery
34	6/24/40		100	45	6	0.8		Heart disease (circulation time, 40 sec.)	
	8/7/40		70	12	8	1.2		Cardiac sclerosis	Illness continues
35			80	40	5	1.8		Portal cirrhosis	Illness continues
36	7/18/40			55	7	0.7		Portal cirrhosis	Illness continues
	8/2/40		80	65	7	0.4			
37			65	10	5	1.0		Portal cirrhosis	Illness continues
38	7/25/40		45	5	6	0.1		Portal cirrhosis, beriberi	
	8/2/40		30	5	7	1.0			Recovery
39			70	35	6	3.2		Portal cirrhosis	Recovery
Hemolytic Jaundice									
40		30	5	2	50	2.6		Arteriosclerosis	Death
41		3	2	0	7	3.8			Recovery
42			42	7	35		Trace		Recovery
Obstructive Jaundice									
43			100	80	40	3.4		Biliary cirrhosis	Recovery
44	2/27/39	100	80	40	7	2.9		Stricture of common duct	
	4/22/39	20	0	0	6	2.9			Recovery
45			85	30	8	1.5		Carcinomatous obstruction, postoperative biliary fistula	Illness continues
Biliary Fistula									
46		30	5	2	7		0.2		Recovery
Essential Lipemia									
47		20	5	0	5	2.6			Recovery
Gall-Bladder Disease									
48		30	7	2	7	2.2		Acute hepatitis (recent)	Recovery
49		3	0	0	7	3.0		Giardiasis	Recovery
50			90	10	10	1.6		Biliary cirrhosis	Recovery

*Watson method.

†Recovery in the cases of chronic cirrhosis means recovery from the attack of acute necrosis.

five minutes for thirty-five minutes. The resultant curves are similar to those given here, but such frequent tests seem hardly necessary.

During this study, no effort was made to perform bromsulfalein-excretion tests during jaundice, — with the exception of cases of hemolytic anemia exhibiting jaundice, — since it has previously been shown[9, 10] that the retention of the dye closely parallels the retention of bile.

In the 60 patients included in this study, the diagnoses were as follows: acute infectious hepatitis, 10 cases; acute toxic hepatitis, 16 cases; chronic cirrhosis, 23 cases; hemolytic anemia, 3 cases; obstructive jaundice, 3 cases; biliary fistula, 1 case; essential lipemia, 1 case; gall-bladder disease, 3 cases.

Figure 1 represents the course of 12 cases of acute hepatitis of approximately two or three weeks' duration followed by recovery. It indicates the time relation between the various liver-function tests. Improvement occurred first in the ester fraction of the total blood cholesterol, then in the hippuric acid excretion and finally in the bromsulfalein retention. The initial rise in urobilinogen output early in the disease was followed by a drop associated with diminished bile in the bowel. After four to seven days of clay-colored stools, a brown stool appeared at the time of clinical improvement. About two days later, there was a secondary rise in the urinary urobilinogen that was usually higher than the first rise and sometimes persisted for two weeks. The interval between the first appearance of a brown stool and the abnormally increased urobilinogen excretion was quite variable, depending on the degree of liver damage. In a case of acute hepatitis lasting six to eight weeks, this interval may be ten days or more. This phenomenon might be due to a deficit in urobilinogen absorption by the liver.

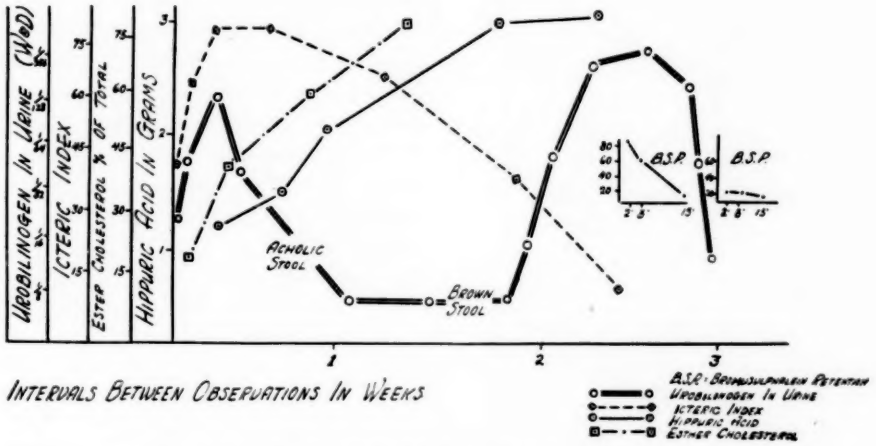

FIGURE 1. *A Composite Chart of Serial Liver-Function Tests in 12 Cases of Acute Hepatitis with Recovery.*

RESULTS

In Table 1, the results are given for 73 tests in 50 patients with disease of the liver in whom more than one type of liver-function test was performed. Fractional bromsulfalein tests in 9 patients, or 18 per cent, showed abnormal retention when other tests were normal. Of these, 4 were acute cases (Cases 6, 7, 10 and 16); 3, cirrhoses (Cases 27, 30 and 39); and 2, obstructive jaundice (Cases 43 and 44). In Case 7, the bromsulfalein test still showed retention — 90 per cent at fifteen minutes — five months after complete disappearance of the jaundice. In a case of beriberi heart disease (Case 38), the serial hippuric acid excretion was below normal, with a normal bromsulfalein excretion.

In 24 per cent of the patients, both the bromsulfalein retention and the hippuric acid or urobilinogen excretion were abnormal. In 58 per cent, both were normal.

A study of bromsulfalein excretion in 10 normal persons showed, in contrast to previous results in dogs,[2] that the dye retention at five minutes amounted to only 50 per cent on the average and never exceeded 60 per cent. The normal human being usually shows no more than 5 per cent retention at fifteen minutes.

Most patients recovering from acute diffuse liver damage show abnormal retention of bromsulfalein in both the early and late phases, improvement occurring first in the late phase. In this same type of case, although the fifteen-minute specimen may show dye retention within normal limits, the five-minute sample may show an abnor-

mally high value, describing a convex curve, and so indicate residual liver damage (Fig. 2). Results of this sort occurred twice in Case 4 and once in Case 7.

In chronic liver disease (Cases 20, 22, 27, 29, 30, 32, 33, 36 and 39), the early removal of the dye followed the pattern of normal persons, whereas the late phase was markedly impaired.

In a small group of cases of residual liver damage receiving sulfonamide therapy, falsely positive Wallace and Diamond tests for urobilinogenuria were obtained in about half the cases, owing to

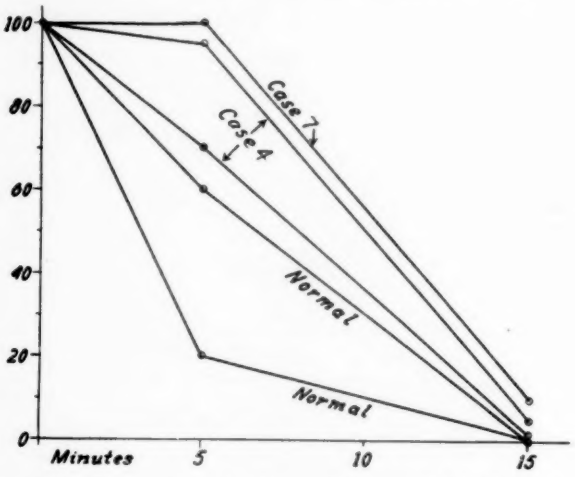

FIGURE 2. *Normal and Abnormal Bromsulfalein-Retention Curves.*

The percentage of retention is plotted against the time in minutes, following the intravenous injection of 2 mg. of bromsulfalein per kilogram of body weight. Note that the abnormal curves are convex.

chemical union of the sulfonamide and Ehrlich's aldehyde in the presence of an acid. In another small group of early to moderately advanced cirrhoses, normal levels of urobilinogenuria were noted in the presence of brown stools. In both types of cases, the fractional bromsulfalein test was of considerable help in distinguishing acute from chronic liver damage.

In Figure 3, the results are given for a fatal case of hemochromatosis (Case 20), which showed improvement in both the icteric index and ester cholesterol percentage during the course of the illness. During protamine insulin therapy, the hippuric acid excretion showed a slight improvement, but the patient shortly became incontinent, and it was therefore impossible to use this test. A fractional bromsulfalein test showed a curve characteristic of chronic liver damage. The patient became progressively worse and died five days later. Autopsy showed the typical findings of hemochromatosis.

In some patients, the hippuric acid excretion remains low at a time when the bromsulfalein test is normal (Cases 22, 37, 38 and 48). A combination of these two tests is always better than either alone.

Two cases of congestive heart failure, pulmonary infarction and jaundice deserve discussion, although they are not included in this series. In spite of multiple tests, there seemed to be no way of determining the degree of liver damage because of the disturbance of circulation and its effect on function tests. At present, it is questionable whether there is any way of evaluating the state of the liver in the presence of circulatory failure associated with pulmonary infarction. One case showed disease of the coronary artery, with multiple pulmonary infarcts and with an icteric index of 80, and normal values for total and ester cholesterol and lipid phosphorus. Four hippuric acid excretion tests in the last three weeks of this patient's life were all below 1 gm. The second case of congestive failure was one of rheumatic heart disease and pulmonary infarction, with jaundice. Bile was absent in six urine specimens. The icteric index was 60, urobilinogen in the urine by the Wallace and Diamond method was repeatedly present in a dilution of 1:64, the hippuric acid excretion remained less than 1 gm., and the

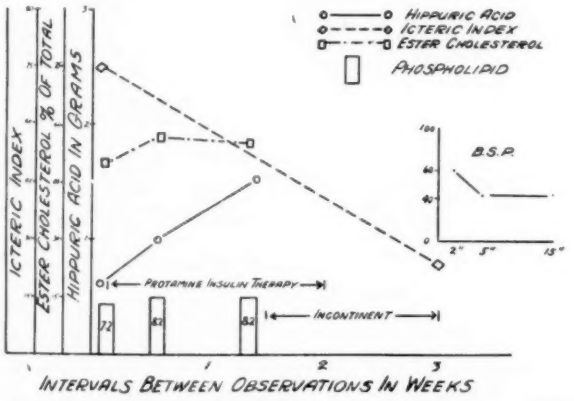

FIGURE 3. *Liver-Function Tests in a Fatal Case of Hemochromatosis, with Acute Hepatitis.*

fractional bromsulfalein showed 70 per cent retention at the end of five minutes, 40 per cent at fifteen minutes, 20 per cent at thirty minutes and 10 per cent at one hour.

In both cases, the elevated icterus is interpreted as being due to hemolysis associated with pulmonary infarction. From the delayed general circulation time associated with congestive heart failure, it may be assumed that there is some degree of impairment of the renal circulation — hence, the low hippuric acid excretion. With a slow circulation time, poor mixing of the intravenously injected dye may be present for fifteen minutes or more after injection.[11, 12] The fact that two

liver-function tests and the icteric index may be disturbed by an extrahepatic process does not mean that these tests are worthless, but rather that they are only of value when used with good clinical judgment. It is fortunate that an estimate of hepatic function in the presence of congestive heart failure and pulmonary infarction with jaundice is not often necessary.

Another case, that of a failing nonjaundiced seventy-year-old patient (Case 8), was studied because of possible liver damage. Her downhill course could have been ascribed to generalized arteriosclerosis, hypertension and cardiovascular syphilis. With a normal circulation time, the bromsulfalein excretion showed 80 per cent retention after five minutes, and 30 per cent after fifteen minutes. Only 1 gm. of hippuric acid was excreted. The two latter findings were the only laboratory evidence of hepatic insufficiency. The icteric index was 5, and the determination of the twenty-four-hour urobilinogen excretion in the urine was within normal limits. At postmortem, the liver showed healing acute yellow atrophy.

Comment

From this study, it is evident that a certain small percentage of previously jaundiced patients show abnormal retention of bromsulfalein in the blood stream for periods varying from several weeks to several months following recovery. The abnormality is best revealed by a study of the serum at intervals of five and fifteen minutes rather than the customary thirty-minute period, since the longer interval usually shows a normal result. A convex curve indicates residual damage even when the fifteen-minute specimen shows no retention.

Soffer and Paulson[13] have shown that the bilirubin-excretion test is a better test of residual liver damage than the half-hourly bromsulfalein test. I have had no experience with the bilirubin test because of its expense, but it would be of interest to compare the bilirubin and fractional bromsulfalein tests in the same patients. Another advantage of the fractional bromsulfalein test is that its performance requires only fifteen minutes, compared with four hours for the bilirubin test.

A discussion of the hippuric acid excretion test on a similar series of cases has already been given in a previous report,[1] so that it requires no further comment.

Conclusions

A modification of the routine bromsulfalein test has been tried and includes the collection of specimens at five and fifteen minutes. In a small group of patients, residual liver damage may be detected for periods varying from several weeks to months after jaundice has subsided. In 50 cases in which other liver-function tests were used, the fractional bromsulfalein test showed abnormal function in 18 per cent when the other tests gave normal values.

A combination of the fractional bromsulfalein and the hippuric acid test is preferable to the use of either alone.

The test was not affected by variations in hydration or by kidney disease. In 3 cases of hemolytic anemia with jaundice, approximately normal results were obtained. The short time required for the fractional test is a distinct advantage.

Congestive heart failure, with its accompanying poor circulation time, makes the results of this fractional test unreliable, because of the prolonged mixing time of the dye in the general circulation, and also confuses the hippuric acid test, because of poor renal function.

Since this paper was submitted for publication, an article by Lucia and Aggeler (*Am. J. M. Sc.* **201**:326–340, 1941) has appeared in which the rose-bengal test has been modified in much the same manner as suggested here for the bromsulfalein test, and in which the new method is compared with the hippuric acid test.

469 Beacon Street

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THE MANAGEMENT OF A BLOOD BANK AT THE MASSACHUSETTS MEMORIAL HOSPITALS*

FRANK E. BARTON, M.D.†

BOSTON

AT a recent clinical meeting of the Boston Surgical Society, considerable interest was shown in the technical management of the blood bank at the Massachusetts Memorial Hospitals. The questions and discussions arising in that demonstration prompted the writing of this paper. No attempt is made to review the history of this subject. A recent survey of the literature on blood banks, with an excellent bibliography, is presented by Douglass.[1]

There are very few active blood banks in New England. The reason for this may be the fallacy that the management of a bank requires the services of several full-time technicians, as well as the expenditure of large sums of money. I shall endeavor to prove that this idea is wrong.

A blood bank must have concrete reasons for its existence and demonstrable evidence of its value. The experience of the Massachusetts Memorial Hospitals is that a blood bank provides immediate availability of blood of various types, a safe blood from the standpoint of the transmission of syphilis, an economical blood (the cost of our transfusions has been materially reduced), a means for the collection of plasma (our outdated blood is converted into and stored as plasma), a lightening of the labors of the visiting staff and interns, and an increased efficiency in collecting blood. Furthermore, it places the responsibility of all transfusions on a director and his associates.

The blood bank at the Massachusetts Memorial Hospitals is made up of two component parts: placental blood bank and adult blood bank.

The placental blood bank was described in a previous article.[2] The bank was instituted in March, 1938. Since the development of the adult blood bank, the placental blood has been used for only two purposes: first, as a source of blood for newborn babies and pediatric cases and, secondly, as a source of blood for plasma.

The management of the adult blood bank is described in detail because of the many requests for this information from hospitals throughout New England.

PERSONNEL OF THE BLOOD BANK

Director. A staff member interested in the subject of transfusion assumes the entire responsibility. He selects and supervises the other members of the transfusion service and manages the blood bank. The director should also stimulate research and progress in regard to transfusions and blood banks.

Operator. The operator or his alternate physically examines all donors and personally performs all venepunctures for the collection of the blood. In this way, an efficient technic is developed.

Technician. A technician has been chosen to specialize in the work of the blood bank. She is a member of the routine laboratory force. The technician is a full-time laboratory worker, and although the duties of the blood bank are her primary interest, she is available for other work. Her duties consist in making hemoglobin determinations and complete blood counts on all donors and personally securing the samples of blood for serologic tests and typing; after collecting the samples, she personally completes their analysis and is responsible for recording all results on the various tags and cards. She also sees that all outdated blood is forwarded to the laboratory for siphonage, and that the plasma is returned to the refrigerator. At the most, this requires three hours a day.

Running nurse. The running nurse is a graduate nurse assigned to the two examining rooms where the clinics for the collection of blood are held. Her station at the clinic is permanent. She has, of course, many other hospital duties, but the blood bank is her chief responsibility. She is schooled in the technic, and it is her duty to see that all apparatus used in the collection of blood is in working order. She prepares the donor, and secures the history and permits before blood is taken.

Supervising nurse. The supervising nurse is a graduate and a member of the training-school office. She is responsible for all dispensing of blood: house officers are not permitted to remove blood from the bank without her permission during the day or without that of the supervisor of nurses on duty at night. It is her duty to see that the blood nearing the outdated period is dispensed first. Each day, the supervisor checks the refrigerator for temperature, and places on the upper shelves the bloods that have been liberated by completed serologic tests and typing. She tests all bloods for time limits, keeps the filing system in order, no

*From the Department of Surgery, Massachusetts Memorial Hospitals.

†Instructor in surgery, Boston University School of Medicine; visiting surgeon, Massachusetts Memorial Hospitals.

tifies the cashier when a patient is to be discharged and has not met his obligation to the bank, and prompts the interns to secure donors for patients who have been given blood but have replaced none in the bank. Briefly, the supervisor keeps the bank solvent, and is responsible only to the director.

Collection of Blood

The two-unit system is used for the blood-collecting clinic: in one room the donor is questioned and examined, and in the other the blood is collected.

Room No. 1. In the history, special emphasis is placed on exanthemas, syphilis, malaria, allergy, tuberculosis, and the time of the last meal and the last transfusion. The donor is prepared on the operating table, with the arm extended on an arm board.

In addition to physical examination, which includes examination of the throat, skin and lymph nodes, the blood pressure, pulse and temperature are taken and a hemoglobin determination and complete blood count are performed. These data are filled in under the heading "Donor" on a special sheet prepared for the transfusion service. This sheet is yellow, as are all records pertaining to the transfusion department. The top of the sheet concerns the history of the recipient and is filled in at the time of transfusion. It consists in data that may be interesting from the standpoint of statistics: the indication for the transfusion, the method used, the amount of blood, the type of blood and the reactions, if any. The serial number is placed on each flask, and a corresponding number on a set of records pertaining to that flask, so that at any time during the year the exact number of transfusions given may be instantly determined. It is hardly necessary to state that if, for any cause, the physical examination or history brings to light some reason why the blood should not be used for transfusion, the donor is excused.

A written permit on a special blank is secured from the donor, giving permission to administer the blood to the patient mentioned in the permit. The permit also states that if, for any reason, the blood is not compatible or is not used for the patient for whom it was secured, the hospital may employ the blood for any other purpose it may see fit. This permit is witnessed.

Room No. 2. The closed system for collecting blood is used. The apparatus includes an aluminum pan (Wearever, No. 2434) wrapped in a sterile covering and containing a three-holed rubber stopper, through which there is a piece of straight glass tubing 10 cm. in length. To this is attached a piece of stiff brown-rubber tubing with a 3-mm. lumen. In the other end of this tubing is inserted a Murphy drip bulb, without the air vent, and to the other end of the Murphy drip bulb, in turn, another piece of tubing is attached. Cotton is placed in the Murphy drip bulb. The operator applies suction by water pump or by mouth to the free end of the tubing. In the second hole of the rubber stopper is placed a right-angle glass tube, and to this is attached a piece of yellow, translucent, acid-cured rubber tubing 65 cm. (26 in.) in length with a 4-mm. lumen. This tubing is directly connected with a 13-gauge or 16-gauge needle, the taking needle. A glass adapter is purposely not used because it causes both constriction in the pipe line and frequent clotting. The translucent tubing serves the same purpose as an adapter, since blood may be

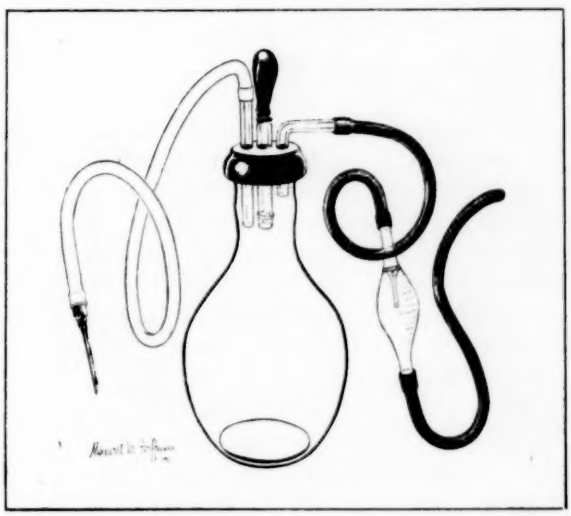

Figure 1. *Apparatus Used for Securing the Blood.*

visualized through the wall of the tubing. In the third hole of the stopper, there is a short section of glass tubing the free end of which is covered with a medicine-dropper bulb. This has been arranged so that if at any time it becomes necessary to add additional citrate to the blood it may be done by inserting a syringe needle through this bulb; by this method, it is unnecessary to detach the stopper. In the aluminum pan, there is also a Fenwal metal and rubber cap, which is inserted in the neck of the bottle at the completion of the collection of the blood, thereby keeping the contents of the bottle airtight. The 500-cc. Fenwal flask in which the blood is collected has a separate sterile wrapping.

After the collecting outfit has been assembled (Fig. 1), a 50-cc. ampule of 2.5 per cent sodium citrate solution is emptied into a sterile glass con-

tainer. By suction, this fluid is drawn into the collecting flask through the needle and the rubber tubing; the flask is then agitated so that its wall is wet by the solution. This amount of sodium citrate is usually sufficient to prevent the coagulation of 450 cc. of blood. If smaller or larger amounts are to be drawn, the volume of citrate solution is varied accordingly.

The Fenwal flask, with its attachments, is placed on a stand below the level of the donor and out of his line of vision — it is important, for psychic reasons, not to allow the donor to see the amount of blood removed. During the collection, the agitation of the flask is minimized. When the desired amount of blood (usually 500 cc.) has been collected, a hemostat is applied to the translucent tubing close to the flask. This tubing is then detached from the glass tubing in the rubber stopper. Samples of blood are collected in two test tubes for serologic tests and typing by simply releasing the hemostat for the tubing. The needle is then removed from the vein. The three-way rubber stopper is removed from the flask, a sterile pipette is inserted, and a sample of the blood and preservative is withdrawn and placed in the third test tube. This test tube is known as the pilot tube, and it is from this tube that all future typing will be performed, thereby eliminating the necessity of entering the flask until it is used for transfusion or its conversion into plasma.

After the completion of the collection of blood, 25 cc. of a 50 per cent solution of dextrose and 25 cc. of distilled water are gently added to the flask containing sodium citrate and blood. When dextrose is added in this amount, the supernatant fluid usually remains perfectly clear and shows no evidence of hemolysis for as long as forty-six days. However, when this preservative is used, the flasks are routinely forwarded at the end of twenty-one days for siphonage to convert blood into plasma. Blood preserved with sodium citrate alone is converted into plasma at the end of eight days.

The refrigerator in which the blood is stored is of special design (General Electric Company, Cabinet No. 2425). With thermostatic control, the temperature is maintained at 38°F. The revolving shelves are very practical, since one thus has access to any flask on the shelf without moving or agitating the containers. The flasks of one type are grouped together on a single shelf. Flasks most recently collected are placed on the lower shelf, to be distributed later when the laboratory work is completed. The refrigerator is located in the room in which the blood collections are made.

Processing of Plasma

From a blood collected to process into plasma, the latter is removed twenty-four hours later, and from blood that had been intended but had not been used for transfusion, on a definite date after collection. When the bank was instituted, a combined siphon and centrifuge method was used. The centrifuge process has been eliminated because the increased yield of plasma was not sufficient to compensate the risk of contamination by an added step in technic.

A very compact and economical cabinet has been constructed to be used while the plasma is being processed. The cabinet is a workbench with a hood attached. In front of the technician is a hinged glass window to prevent breath and dust contamination. Beneath the window is a 20-cm. opening to admit sterile gloved hands. A sterile gown is worn. The top of the hood is closed to eliminate active currents of air. Attached to the upper part of the hood is a Westinghouse Sterilamp.* The cabinet is portable and should be placed in a clean room away from traffic.

The transfer of plasma from the blood flasks to the pooling flask is carried out in a closed system. The Fenwal stopper is removed from the flask of blood. A two-holed rubber stopper is substituted. A glass tube passing through one opening is adjusted to a level just above the line of demarcation between plasma and cells. The second glass tubing acts as an air vent. A 2-liter Fenwal flask is used for pooling the plasma. This large flask is connected to the flask of blood by rubber tubing. A two-holed rubber stopper is inserted in the pooling flask, and through the second opening is a glass tube with a rubber-tube attachment for suction. Suction is produced either by water pump or by mouth. Plasma is separated from bloods of various types and collected in the pooling flask. The flask is agitated, and the process is reversed to transfer the plasma from the pooling flask to the storage bottle.

Merthiolate (Lilly) is added to each batch of pooled plasma. A 1 per cent stock solution is prepared by adding 1 gm. of Merthiolate, together with 1.4 gm. of borax as a buffer, to 100 cc. of distilled water; 1 cc. of this solution is added to every 100 cc. of plasma. A sample of each batch of

*The Westinghouse Sterilamps are essentially monochromatic generators of ultraviolet radiation, which is highly bactericidal. The tube is set for a radiation of 28.8 microwatts per minute as measured, by a Tantalum photoelectric cell. The tube is checked monthly, and if the intensity drops, the regulator may be adjusted to maintain a constant intensity. The tube is placed 75 cm. (30 in.) above the table. The ultraviolet ray will not penetrate glass, and therefore does not affect the blood, or the eyes of the technician. In preparation for processing the plasma, a sterile drape and then the flasks and apparatus to be used are placed on the bench. The Sterilamp is lighted, and after half an hour, the technician begins her operation, working under the lighted lamp.

plasma is obtained for culture, and the latter is incubated for at least two weeks.

The plasma is stored in the refrigerator in 500-cc. straight-walled flasks sealed with Fenwal rubber and metal caps.

The pooled plasma can be used without typing and will keep indefinitely if stored in an airtight container at 38°F. without exposure to light.

Banking

Credit. Seventy per cent of cases needing transfusion can be predicted days before the actual administration of the blood. These patients are requested to have one or more donors, according to the need, report to the blood clinic at a scheduled time. The blood is collected irrespective of type, and to this patient is credited the amount donated. If for any reason the full supply of blood collected is not used, it becomes the property of the bank.

Debit. If, because of an emergency, a patient is required to have a transfusion, the blood for which has been furnished by the bank, this patient is in debt to the bank for the amount given and must secure donors for the next banking day. The filing system compiled by the supervisor is responsible for keeping the bank solvent.

Banking hours. It is the policy of the blood bank to collect on certain afternoons and evenings. This variation in time allows for different working hours of the donors and has worked out very satisfactorily. No blood is secured from donors at any other time, except in emergency.

Cost of transfusion. A flat charge is made for each transfusion according to the means of the patient. This charge is comparable to any operating-room fee. Many indigent patients who are unable to secure donors for one reason or another are now transfused without expense to the hospital. The availability, the safety and the decreased cost per patient have materially increased the number of transfusions. As plasma becomes available, there will probably be an increasing trend toward its use.

Social Aspects

Approximately 5 per cent of unsuspected positive serologic reactions with bloods from donors have been encountered. Afflicted donors are requested, in a carefully worded letter from the social-service department, to return to the hospital. The reason for this conference is not divulged. The social-service worker verbally informs the donor of his misfortune and arranges for his treatment.

Summary

The management of the blood bank at the Massachusetts Memorial Hospitals is outlined. Emphasis is placed on specialization in the collecting and handling of the blood and the processing of the plasma. Experience with a blood bank has shown that the cost of the personnel and equipment is not prohibitive, that the ease and frequency of transfusion are increased, and that the safety factors of transfusion are greatly improved.

29 Bay State Road

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AN EVALUATION OF PERITONEOSCOPY*

With Particular Reference to the Diagnosis of Abdominal Tumors

WALTER E. GARREY, M.D.†

BOSTON

PERITONEOSCOPY, or visualization of the abdominal cavity, is far from new. However, following increased experience with an improved instrument, it is pertinent to inquire into the results that have recently been obtained. The physician wishes to know when peritoneoscopy is worth while and what information it provides that cannot be obtained in other ways. He wishes to know how much discomfort, expense and risk it involves for his patient. He wishes particularly to know how often the information obtained will materially alter the treatment.

It is not generally appreciated that this method of abdominal diagnosis is thirty-nine years old. The historical aspects have already been well reviewed by Ruddock.[1] In 1901, Kelling,[2, 3] of Dresden, first demonstrated the observation of abdominal viscera on a dog, using pneumoperitoneum and a cystoscope. He later examined 2 patients by this method, one a case of ascites and the other a case of gastric carcinoma. Jacobaeus[4] developed an improved instrument and used the same technic. To illustrate the type of work done by these pioneers, Jacobaeus's report in 1913 of 138 such examinations included the diagnosis of 17 cases of liver cirrhosis, 31 cases of malignant abdominal tumor, 10 cases of tuberculous peritonitis, 3 cases of syphilitic liver and 9 cases of Pick's disease. Nordentöft[5] reported in 1912 the endoscopic examination of female pelvic organs with the patient in the Trendelenburg position. The instruments then used were too short to be certain of inspecting both the upper and the lower abdominal cavity through one insertion, had a narrow field of vision, and did not permit obtaining a biopsy.

These faults were overcome in the Ruddock[1] instrument, which has been in use for six years. Ruddock has reported 500 examinations with it, and is soon to report 1000 additional examinations. There is no other series nearly so large, but Benedict[6, 7] has reported 50 and later 100 cases, and Thieme[8] last year published a critical survey of peritoneoscopy, based on 50 cases. The following data are based on 75 cases.

*From the Joseph H. Pratt Diagnostic Hospital and the Surgical Service, Faulkner Hospital.

†Peritoneoscopic consultant, Joseph H. Pratt Diagnostic Hospital; associate staff member, Faulkner Hospital.

METHOD

The detailed description of technic has been well covered by Ruddock[1] and is therefore only briefly outlined. A small block of the abdominal wall, preferably in the mid-line just below the umbilicus, is anesthetized by novocain infiltration. A 1.5-cm. skin incision is made. A pneumoperitoneum is induced with a small blunt trochar and cannula. A larger trochar with cannula, the latter constituting a sheath for the optical instruments, is then introduced through a nick in the anterior fascia. The instrument thus comes to lie in the space created by the insufflated air, between the abdominal wall and the abdominal viscera.

In the average case, inspection reveals the anterosuperior surface of the liver and variable amounts of the inferior liver surface near the edge. The dome of the gall-bladder fundus can almost always be viewed. The lower anterior gastric surface is seen. How much of the upper stomach is visualized depends on the degree of ptosis. The anterior surface of the great omentum and the surface of those coils of bowel not covered by it may be inspected. The pelvis can be well explored only with the patient in a very steep Trendelenburg position. In women, the uterine fundus, proximal tubes and anterior surface of the broad ligaments are readily seen. The fimbriated ends of the tubes and the ovaries may at times be prolapsed behind the broad ligaments; in these cases they are difficult to see.

The ambulatory patients in my series have averaged a thirty-six-hour stay in the hospital. In a few cases in which there was no biopsy, the patients have remained only ten hours. With increasing experience, I am convinced that there should be negligible discomfort, comparable to a well-executed abdominal paracentesis. To accomplish this, three things are necessary. First, the block of the abdominal wall, at least 5 cm. square, must be thoroughly infiltrated, with particular attention to using sufficient novocain beneath the fascia and below each rectus muscle to anesthetize the peritoneum. Secondly, the optical instrument must be gently moved, so that it does not jolt and, if possible, does not touch visceral surfaces. Thirdly, an effort must be made to press out most of the air at the end of the examination.

For satisfactory results, the facilities of an operating room are needed. An operating table that will tip steeply either way, suction and electrocautery are recommended.

I have at various times inserted the instrument into each of the four quadrants of the abdomen and the epigastrium. The cardinal rule is to keep far away from old laparotomy scars to which the hollow viscera might be adherent. The literature records a few cases of penetration of bowel due to an adherent viscus; all were detected and none were fatal. It is imperative that the pneumoperitoneum needle move freely within the abdomen to ensure that no emphysema of omentum or of abdominal wall occurs.

Contraindications

Peritoneoscopy should never be used in the possible presence of bacterial infection in the free peritoneal cavity. Except in the diagnosis of ectopic pregnancy (Hope[9]), it has no place in the diagnosis of acute abdominal conditions. It has been used to see if an abdominal-wall stab wound penetrated through the parietal peritoneum (Hamilton[10]). This seems safe only in an early case, and then only with preparations to follow at once with a laparotomy if penetration through all the layers of the abdominal wall has occurred. The pneumoperitoneum may produce some reduction of vital capacity. If there is an appreciable amount of hydrothorax, the fluid should be removed before peritoneoscopy. Naturally, decompensated heart disease is a contraindication. Age and senility alone are no contraindication; 14 of the patients in this series were over the age of sixty, and 2 were over the age of eighty.

Complications

In the 75 cases, there has been no mortality attributable to peritoneoscopy. There has been no complication since the second case, in which sepsis occurred in the abdominal wall as the result of contamination from the wound of a previous paracentesis. Complications listed in the literature are: emphysema of the abdominal wall,[6, 7] hematoma in the wound of entrance[8] and bleeding from the site of biopsy.[1] Hematoma in the abdominal wound in cases with liver damage may be prevented in the future by use of vitamin K. Electrocoagulation of biopsy sites must be carefully performed if any appreciable bleeding occurs.

Field of Usefulness

There are four broad groups of conditions in which peritoneoscopy may confirm a diagnosis, render an exploratory laparotomy unnecessary, and aid materially in giving a prognosis: namely, to determine the presence, extent, nature and operability of cancer; to demonstrate the nature and extent of pelvic tumors and of lesions of the female pelvic organs; to make the differential diagnosis of ascites; and to make the differential diagnosis of liver disease. Naturally these groups overlap. In this series, the following diagnoses were correctly made:

DIAGNOSIS	NO. OF CASES
Malignancy	
Metastatic carcinoma in the liver	11
Peritoneal carcinomatosis	6
Gastric carcinoma, without metastases	5
Metastatic fibrosarcoma of the peritoneum	1
Melanotic sarcoma in the liver	1
Primary hepatoma of the liver	1
Tumors of the female pelvic organs	
Ovarian carcinoma	7
Malignant ovarian cyst	1
Benign ovarian cyst, with twisted pedicle	1
Benign ovarian cyst	1
Fibroid uterus	1
Differential diagnosis of ascites and liver disease	
Cirrhosis of the liver	14
Syphilis of the liver	1
Splenomegaly, without cirrhosis	1
Fatty infiltration of the liver	1
Inflammatory mass below the liver	1
Carcinoma of head of the pancreas (presumptive)	1
Tuberculous peritonitis	1
Multiple adhesions	1

In the remaining 18 cases, peritoneoscopy showed the visualized portion of the abdominal cavity to be normal. These patients had hypernephroma, calcified mesenteric masses, retroperitoneal tumors, vaginal carcinoma, rectal carcinoma and so forth. Two obese patients, thought probably to have abdominal tumors, were shown to have none.

Early leaking of blood from an ectopic pregnancy is diagnosable with great accuracy.[9] The peritoneoscope has been used to sterilize the female by electrocoagulation of the isthmial portion of the Fallopian tubes under direct vision (Anderson[11]). This attempt at operative peritoneoscopy has even been carried farther in suturing the internal orifices of inguinal hernia under direct vision (Ruddock, quoted by Sawyer[12]). It seems that these operative procedures are more surely and safely performed by laparotomy. However, I have had no personal experience on which to base such a conclusion.

Accuracy of Diagnosis

There is no case in which I am, as yet, aware of an erroneous diagnosis; biopsies were obtained

in 15 cases. In 2 cases, however, a conclusive diagnosis could not be made. One patient was a man with ascites who previously had had extensive gastric surgery for peptic ulcer. Because of numerous adhesions, only a small portion of the right upper peritoneal cavity and liver surface was available for inspection. In the second case, a carcinoma of the gall-bladder area was suspected, but the omentum had become densely adherent to both gall bladder and liver, and hence a satisfactory view could not be obtained. In the second case, exploratory laparotomy was advised and performed, and a carcinoma of the gall bladder, with metastasis, was found.

Thieme[8] has pointed out that the largest groups of cases for peritoneoscopy are those in which the diagnosis is already strongly suspected and only absolute confirmation is wanting. There is another small group of cases in which every diagnostic procedure short of exploratory laparotomy has failed to give the diagnosis. In these cases, the result of peritoneoscopy may be quite dramatic. Case 1 is illustrative.

Case 1. Mrs. B. B. (J. H. P. D. H. 5350), a 46-year-old housewife, entered the hospital complaining of weakness and fullness in the pit of the stomach for over a year. One year previously, she had had frequent and profuse menstrual periods and had been examined at a clinic, where fibroids were found. Five months before entry, she became troubled by indigestion, and the vaginal bleeding ceased. Four weeks prior to entry, she had lancinating pain in the right upper quadrant lasting for several hours. There had been definitely increasing dyspnea on exertion. Physical examination showed a palpable liver, a fibroid uterus, a slight anemia and a slight and irregular fever. X-ray examination of the gall bladder, stomach and colon was negative. On entry, x-ray films of the chest were negative, but later showed fluid in the right chest.

Peritoneoscopy confirmed the diagnosis of a fibroid uterus. The stomach, omentum and peritoneal wall were normal, but on the superior surface of the liver two yellow nodules, several centimeters in diameter, were seen that had the appearance of metastatic carcinoma. A biopsy report indicated carcinomatous metastasis to the liver; the primary source was not known. This patient gradually failed and died.

In this patient, x-ray examination and all other diagnostic studies failed to give the diagnosis, yet metastatic carcinoma was present. Two other cases were identical.

In 2 cases, intra-abdominal cancer was strongly suspected, but peritoneoscopy fortunately proved the presence of benign lesions. One was a case of syphilitic liver, and the other an intraomental abscess of unknown etiology; an abstract of the latter follows.

Case 2. J. G. (J. H. P. D. H. 327–395), a 40-year-old Lithuanian, entered the hospital complaining of steady pain in the right upper abdomen of 10 days' duration. No jaundice, nausea or other symptoms were noted. Seven and a half years previously, however, he had an attack of right upper abdominal pain followed by jaundice. This was thought to be due to acute hepatitis. On examination, he had a rounded, exquisitely tender, right-upper-quadrant mass and ran a slightly elevated temperature (average 100.5°F.). He had a moderate anemia (hemoglobin 63 per cent), and white-cell counts ranged from 7000 to 10,000. He was thought possibly to have either a hydrops of the gall bladder or a cancer. However, an entirely normal cholecystogram was obtained.

In this case, the peritoneoscope was introduced in the left upper quadrant. The inferior surface of the liver was entirely normal. Numerous inflammatory adhesions in the right upper abdomen formed a curtain between the abdominal wall and the inner edge of the liver, and a large mass of omentum was densely adherent to the abdominal wall. Pericholecystic abscess seemed the likeliest diagnosis, yet could hardly have been present, since the Graham test was normal. An operation was performed, and a necrotic inflammatory mass was found in the omentum. Its origin was undetermined but thought possibly to be the result of a pancreatitis.

Here again, short of exploratory laparotomy, no diagnosis was possible other than by the means of peritoneoscopy. However, in this case a laparotomy was eventually needed.

General Considerations

Carcinoma of the Stomach

Some writers believe that every case of carcinoma of the stomach should be examined by peritoneoscopy before operation to determine the presence or absence of peritoneal and liver metastasis. If a palliative operation is indicated in any case, I consider peritoneoscopy unnecessary. Moreover, the operability in relation to posterior fixation and retroperitoneal metastases cannot be determined by peritoneoscopy. However, it is true that a small growth may already have hepatic metastases, whereas a large growth may have none and yet be quite operable. Peritoneoscopy may give strong evidence for either of these situations.

Case 3. A. N. (F. H. 57649), a 62-year-old man, entered the hospital complaining of weakness, epigastric distress and evening anorexia of 2 weeks' duration. There was no nausea or vomiting, and a loss of only 6 pounds in weight. X-ray study showed a small carcinoma in the antrum of the stomach. Peritoneoscopy disclosed some confluent yellow masses in the left lobe of the liver typical of metastatic tumor, and a biopsy was obtained. No operation was performed, and the patient died 4 months later.

This man had a small carcinoma, with a short duration of symptoms, yet peritoneoscopy disclosed liver metastases. He later died without developing symptoms that surgery could have alleviated.

Case 4. L. S. (F. H. 56330), a 63-year-old carpenter, complained of weakness, weight loss and tarry stools of 10 months' duration. The patient was emaciated. A large mass was palpable in the epigastrium. X-ray examina-

tion showed a large filling defect of the antrum of the stomach. Peritoneoscopy readily visualized the liver, and no metastases were present. No metastases were seen on the peritoneum, and the tumor did not appear to have come through the gastric surface. The patient was operated on, and an extensive resection performed, after which he did well.

In contrast to the patient in Case 3, this man had a large growth of considerable duration. Symptoms were compatible with the presence of metastases. Peritoneoscopy gave encouragement to preparation for an extensive resection, which was carried out successfully.

Tumors of the Female Pelvic Organs

In the majority of women, peritoneoscopies have been performed for the purpose of confirming by biopsy a strongly suspected diagnosis of ovarian

FIGURE 1. *Ovarian Cyst and Female Pelvis as Seen through the Peritoneoscope (Case 6).*

carcinoma. Some of the patients had ascites, and in 2 cases the pelvic tumors were not palpable from below; the peritoneoscope was consequently the only method of making a diagnosis and enabling x-ray treatment to be started.

CASE 5. Mrs. M. D. (F. H. 13161), a 49-year-old housewife, entered the hospital complaining of a swollen abdomen of 7 months' duration. Examination showed some evidence of weight loss. No pelvic masses were felt. Repeated abdominal taps failed to give a diagnosis on spun sediment. Peritoneoscopy showed a nodular mass typical of ovarian tumor involving the left broad ligament, and a biopsy showed a papillary adenocarcinoma.

Cirrhosis of the liver was considered in this case, since no pelvic tumor could be felt. The diagnosis of a radiosensitive pelvic neoplasm was established.

CASE 6. Mrs. J. R. (F. H. 57461), a 43-year-old housewife, had complained, for 3 months, of an intermittent dull pain in the left flank. The catamenia were normal, and no genitourinary or gastrointestinal symptoms were noted. Examination showed an enormously obese woman with an overhanging panniculus of abdominal fat. An indefinite mass was at times felt high in the left pelvis. Abdominal x-ray examination was negative.

Peritoneoscopy showed a 10-cm. ovarian cyst, with a partial clockwise twist in its pedicle, but with no impairment of its blood supply. The other pelvic organs were normal.

The presence of an abdominal tumor was confirmed, and its nature determined, in an extremely obese woman in whom the very existence of the tumor was in some doubt.

Jaundice and Liver Diseases

Peritoneoscopy is of greatest help in patients with jaundice and liver disease. A direct visualization of the liver and, if necessary, a biopsy give a far more accurate diagnosis than one based on clinical history and tests of liver function. The picture of cirrhosis, in contrast to the normal smooth liver surface, is as clear through the peritoneoscope as it is in the post-mortem room. In cases of ascites without jaundice, and cases of intermittent jaundice with or without pain, the peritoneoscope will rule cirrhosis in or out. If a laparotomy must follow, to examine the pancreas or bile ducts, it will be performed with the conviction of its urgent need.

CASE 7. R. M. (J. H. P. D. H. 5143), a 58-year-old plumber, had felt weak and had tired easily for 14 months. Twelve months before entry, slight jaundice had appeared, and he consulted a clinic. All studies, including a gastrointestinal series, were negative. The degree of jaundice varied during the ensuing year; at times there was none. A medical consultant believed that statistically there was a 70 per cent chance that the trouble was due entirely to cirrhosis.

Peritoneoscopy showed an absolutely smooth liver surface and a greatly enlarged gall-bladder fundus. This was considered strongly suggestive of an obstructing lesion of the lower biliary ducts.

A subsequent barium meal showed some narrowing of the second portion of the duodenum. At operation, a carcinoma of the head of the pancreas was found.

SUMMARY AND CONCLUSIONS

Peritoneoscopy has been safely performed in 75 cases. The gross pathologic lesions were identi-

fied and a correct diagnosis returned in 55 cases. In 2 cases, both complicated by adhesions, it was impossible to be certain of the diagnosis. Fifteen biopsies were performed, all of which showed either a malignant tumor or a diseased liver. In

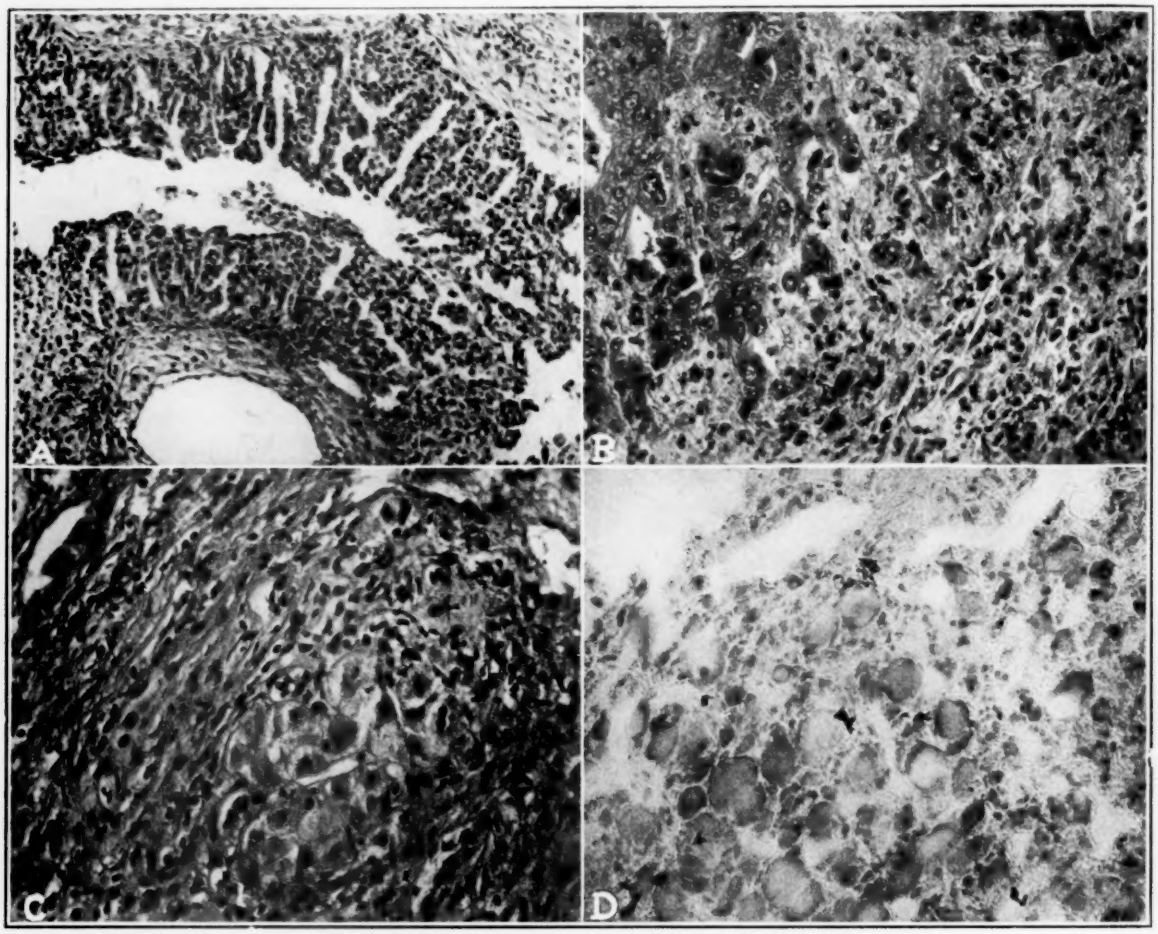

FIGURE 2. *Biopsy Specimens Obtained through the Peritoneoscope.*

A — *carcinoma of the ovary;* B — *metastatic carcinoma of the liver;* C — *cirrhosis of the liver;* D — *fatty degeneration of the liver.*

25 per cent of these cases, the findings fundamentally altered the treatment. In the remainder, accurate confirmation of a suspected diagnosis was obtained.

Peritoneoscopy is not merely useful: it is essential to the study of abdominal tumors and liver disease if needless laparotomies are to be avoided. It involves only a fraction of the expense or morbidity of a major operation.

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MYOMECTOMY DURING PREGNANCY*

ROY J. HEFFERNAN, M.D.†

BROOKLINE, MASSACHUSETTS

ALTHOUGH fibroids frequently coexist with pregnancy, they rarely cause serious complications. Pierson[1] found only 191 cases, or 0.6 per cent, of clinically important fibromyoma in 30,836 consecutive pregnancies analyzed at the Sloane Hospital for Women.

The uterus is usually very tolerant of the presence of fibroids, and I have observed many women with large tumors who progressed without difficulty through pregnancy, labor and the puerperium. The large growths are more frequently seen in elderly primiparas or in multiparas whose last baby was born several years previously. Fibroids that are palpated low on the uterine wall early in pregnancy may, as the uterus enlarges, be retracted out of the pelvis so that they offer no obstruction to labor. Intraligamentary and cervical fibroids usually do remain pelvic, however, and may necessitate abdominal delivery.

The occurrence of spontaneous abortion and premature labor is high. Pierson found it in 24.1 per cent of his series. Torsion of the pedicle may occur. A fibroid in the posterior wall may prevent replacement of a retroverted or retroflexed uterus. In 1930, I[2] reported the suspension of an incarcerated, two-months-pregnant uterus with a large fibroid on the posterior wall. All attempts at replacement by conservative methods had failed, and miscarriage seemed imminent. The patient was delivered at term, and a myomectomy was performed four months later.

The chief complication during the prenatal period, however, is degeneration, the commonest type of which is so-called "red degeneration." This may occur with or without secondary hemorrhage in the tumor and is always associated with pain. The morbid process does not as a rule progress to actual death of the cells, but in neglected cases liquefaction and necrosis may ensue. Following this, the aseptic devitalized tissue may become infected through the blood stream or by contiguity from adherent intestine. The exact cause of this degeneration is not known, but it is believed to result from an interference with the blood supply of the fibroid by changes occurring in the pregnant uterus. This would explain why degeneration of these tumors is commoner during the puerperium. The post-partum administration of ergot should be withheld in these patients unless subinvolution or excessive flowing makes its use imperative.

Clinically, the onset of degenerative changes in the tumor is marked by pain, usually severe, over the site of the growth. An elevation of temperature of one or two degrees is usually noted, accompanied by moderate leukocytosis. Vaginal bleeding may or may not occur. In mild cases, the symptoms subside under rest and sedatives to control the pain. Conservative treatment should be given a thorough trial, but if the pain increases and the temperature and leukocyte count indicate that the degeneration is progressing unfavorably, surgery should be considered.

A report of 4 cases in which the fibroid was enucleated during pregnancy is presented.

CASE REPORTS

CASE 1. Mrs. T., a 38-year-old woman, had been married 9 years and had never been pregnant. Her last regular period began on May 12, 1930. She flowed moderately from July 7 to 9 and then stained for 3 weeks. There was no pain or cramps, and she did not pass clots.

The patient had had no serious illnesses since childhood, but a herniotomy and hemorrhoidectomy had been performed 12 years previously.

On September 3, she developed severe pain in the left lower quadrant and began to flow moderately. On examination, the abdomen was relaxed, and a tender mass could be felt in the left lower quadrant. Vaginal examination revealed a primiparous introitus, with a slight bloody discharge. The fundus was in good anterior position and was enlarged to a size consistent with a 3 months' pregnancy. A firm, very tender mass, apparently attached to the uterus, could be felt in the left vault.

The temperature was 99.8°F., the pulse 96, and the respirations 22. The white-cell count was 12,500. The patient was admitted to the Trumbull Hospital. The following day, the pain had increased in severity; the temperature was 100°F., the pulse 98. The vaginal flowing persisted. On September 8, the white-cell count had risen to 16,000. The flowing increased, and two large clots were passed. The pain in the left lower quadrant became severer and could not be entirely controlled by sedatives. Laparotomy on that date revealed a uterus the size of a 3 months' pregnancy, with a mottled, congested, apple-sized fibroid on the left anterior wall. Myomectomy was performed. Pathological examination of the tumor revealed red degeneration with marked small round-cell and polymorphonuclear infiltration. The following day, the patient was free from pain, and on the 3rd postoperative day the vaginal bleeding stopped and did not recur. Recovery was uneventful, and pregnancy progressed normally until March 14, 1931. On that date, the membranes ruptured at 3 a.m., and the patient

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†Instructor in gynecology, Tufts College Medical School; visiting gynecologist and obstetrician, Carney Hospital.

was admitted to the Massachusetts Women's Hospital. After 8 hours of ineffectual labor, a diagnosis of cephalopelvic disproportion was made, and a transverse cervical cesarean section was performed. On inspection, the myomectomy scar was found to be firm. A normal 10-pound, 4-ounce, baby was delivered, and after a normal convalescence the patient left the hospital on the 14th day.

Case 2. Mrs. M., a 34-year-old woman, was seen in consultation at St. Margaret's Hospital on July 3, 1930. She had had two full-term normal deliveries, the last 5 years previously. Both children were living and well, and there had been no miscarriages. There had been no serious illness and no operations. The last regular period began on April 10, but there had been some irregular flowing off and on since that date and the patient did not believe that she was pregnant. On July 2, a laparotomy had been performed, and the uterus was found to be enlarged to a size consistent with a 2½ months' pregnancy. It was soft and blue, with a fibroid the size of a baseball growing from the fundus. A myomectomy was performed. When I saw the patient the following day, there was a slight bloody vaginal discharge, which ceased after 3 days. On July 12, vaginal examination revealed a uterus the size of a 3 months' pregnancy, with the fundus in good anterior position.

No further flowing occurred, and pregnancy proceeded normally to January 14, 1931. On that date, the patient was awakened at 5 a.m. by labor pains recurring every 5 minutes. She was admitted to St. Margaret's Hospital at 5:46 a.m. and delivered precipitately 6 minutes later. The normal infant weighed 7 pounds, 8 ounces, and the mother made an uneventful recovery.

Case 3. Mrs. M., a 35-year-old woman, had been married 6 years. She had had no children or miscarriages. Her chief complaint was severe pain in the right lower quadrant of 2 days' duration. The last regular period began on June 27, 1931. On October 2, there had been a slight show of blood, with slight pain in the right lower quadrant. Two days later, the flowing increased, the pain became severer, and the patient was admitted to the Carney Hospital.

An attack of rheumatic fever, which did not affect the heart, was experienced in 1922. This was followed by a tonsillectomy, and there had been no recurrence. A hemorrhoidectomy had been performed 1 year previously.

On examination, there was marked tenderness in the right lower quadrant, and an indefinite mass could be felt, apparently attached to the uterus. There was no muscular spasm. On vaginal examination, the fundus was found to be enlarged to the size of a 3 months' pregnancy and was in good anterior position. There was a slight, steady, bloody vaginal discharge. On admission the temperature was 100.2°F., the pulse 94, the respirations 20, and the leukocyte count 12,000. The following day the flow increased, the temperature rose to 101.4°F., and the pain became severer.

On October 6, there was a steady bright-red vaginal flow, and the mass in the right lower quadrant was exquisitely tender. The white-cell count had risen to 15,600. Laparotomy revealed a uterus the size of a 3½ months' pregnancy, with a mottled, egg-sized fibroid protruding from the right anterior wall. A fibroid about half that size was seen on the left anterior surface of the uterus near the bladder reflection. The larger fibroid was enucleated. It extended well into the wall of the uterus, and a small area of amniotic sac could be seen glistening in the depths of the uterine wound after the tumor had been removed. A few deep sutures were carefully placed, and the uterine incision closed. The smaller tumor was enucleated without difficulty. The patient made an uneventful recovery, and there was no vaginal bleeding after the 4th postoperative day.

Pregnancy progressed normally to term. On April 21, 1932, the patient was 2 weeks overdue. Because of cephalopelvic disproportion, on April 22, the patient was delivered by transverse cesarean section. The baby weighed 9 pounds, 6 ounces. The myomectomy scars were inspected and found to be firm. The patient made an uneventful recovery and was discharged 2 weeks later.

Case 4. Mrs. C., a 39-year-old primipara, was seen in consultation with Dr. Chester Goodnow, of Franklin, Massachusetts, on October 31, 1939. Her last period began on March 21, and the expected date of confinement was December 28. For the previous month, the patient had had increasing discomfort and pain in the right flank. For 2 weeks, the pain had been so severe that the patient was unable to sleep. There had been no nausea or vomiting, and no flowing of blood since the last period.

The patient had always been well since childhood, and there had been no operations.

On examination, the fundus was found to be 4 fingerbreadths below the ensiform; the fetal heart was heard in the left lower quadrant, and the rate was 144. A tender mass the size of an orange, apparently attached to the uterus but freely movable, could be felt about 8 cm. above the anterosuperior spine of the ilium. The tumor was exquisitely tender. The temperature, pulse and respirations were normal. The blood pressure was 136/84, and urinalysis was negative. On vaginal examination, the cervix could be palpated high in the vagina, and there were no pelvic masses or tenderness. The patient was anxious to have a normal, full-term baby, but said that she could not stand the pain any longer and requested that something be done.

The patient was admitted to the Milford Hospital on November 2. On the following day, laparotomy revealed a mottled, congested, pedunculated fibroid. A myomectomy was performed. An ampule of Progestin was administered daily for 4 days, and then twice a week for the next 2 weeks. Capsules of wheat-germ oil were also prescribed for a period of 4 weeks.

Pregnancy progressed without further incident, and the patient entered the Milford Hospital in labor on December 30. A normal, 7-pound, 4-ounce baby was delivered by low forceps by Dr. Goodnow. The post-partum period was uneventful, and the patient was discharged on the 13th day.

Summary and Conclusions

Fibroid tumors of the uterus usually have no harmful effect on a coexisting pregnancy.

The patient should be kept under careful observation for complications such as miscarriage or premature labor, obstruction to the descent of the presenting part and degeneration of the fibroid.

So-called "red degeneration" of the tumor is the type usually found, and it occurs most frequently during the puerperium, probably because involution disturbs its blood supply. Degeneration may also occur during the prenatal period. Its onset is

always marked by pain, occasionally accompanied by fever and leukocytosis.

When the degeneration is slight, the symptoms may be relieved by medical treatment, but in the severer types the tumor should be removed. Interruption of the pregnancy should not result from the operation. On the contrary, myomectomy seems to prevent miscarriage.

Corpus-luteum hormone and wheat-germ oil should be administered prophylactically, whether the fibroid is treated conservatively or removed.

Four cases of myomectomy during pregnancy, with delivery at term, are presented.

1101 Beacon Street

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MEDICAL PROGRESS

CHEMOTHERAPY OF PNEUMONIA*

With Special Reference to the Present Status of Sulfadiazine

MAXWELL FINLAND, M.D.†

BOSTON

ANY review of recent progress in the treatment of pneumonia must concern itself primarily with chemotherapy. New developments continue to take place rapidly in this field. Lord's[1] summary in 1939 covered the introduction of sulfonamide drugs in the treatment of pneumococcal pneumonias. He concluded that sulfanilamide, the first important chemical of the group to be widely used in this country, although it had some value in the treatment of pneumonia was less effective and likelier to produce toxic effects than sulfapyridine. The latter had already received quite extensive clinical trial at that time, and the favorable results of its use were fully corroborated in many further reports[2] collected from the literature during the following year.

Results of Sulfathiazole Therapy

Sulfathiazole made its appearance shortly before the last review.[2] The preliminary clinical observations at that time indicated that this drug was less toxic than sulfapyridine, particularly with respect to nausea and vomiting, which were the most frequent and very disturbing features of sulfapyridine therapy. The two drugs appeared to be about equally effective in the treatment of the pneumococcal pneumonias.

Mortality

Numerous reports dealing with sulfathiazole therapy have appeared during the past year. The pneumonias in adults treated with this drug by a number of different authors[3-15] include 1045 cases of pneumococcal pneumonia, with 98 deaths, a mortality of 9.4 per cent. These cases also include patients (about 9 per cent of the total) who received serum in addition to sulfathiazole, usually because of inadequate response to the drug. Also included are cases treated with sulfamethylthiazole, which was found to have a very similar action but which, owing to the development of occasional cases of peripheral-nerve lesions and even encephalopathy[16, 17] resulting from its use, was subsequently withdrawn from further clinical trial. A few authors[3-9] have also included comparable and contemporaneous cases from the same clinics treated with sulfapyridine, alone or with serum, both used in about the same manner as in the sulfathiazole-treated cases. There were 1501 such sulfapyridine-treated cases, with 204 deaths, a mortality of 13.7 per cent. Bacteremia was just as frequent in either group, — 15.2 and 15.3 per cent in the patients treated with sulfathiazole and sulfapyridine, respectively, — but the mortality in these bacteremic cases was 25.2 per cent among the former as compared with 32.6 per cent in the latter.

In general, individual reports have indicated that the effect on mortality and on the clinical course in adults was about the same or slightly better with sulfathiazole as compared with sulfapyridine. Some writers[6, 8] have noted a more rapid defervescence in sulfapyridine-treated cases, but this may have been due, at least in part, to the antipyretic effect of this drug, which either is lacking or is less apparent with sulfathiazole.[18]

Results in Children

In the pneumonias of infants and children, also, the effects of these two drugs have been very similar.[19-22] In the largest series,[20] the mortality

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*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

†Assistant professor of medicine, Harvard Medical School; chief, Fourth Medical Service, Boston City Hospital; assistant physician, Thorndike Memorial Laboratory.

was 4 per cent in patients under the age of two years and 2 per cent in those over two years. Patients who were moribund on admission and died within twenty-four hours of entry to the hospital were also included. The latter cases accounted for about half the fatalities. The average duration of fever was almost exactly the same with the two drugs.

Toxicity

Sulfathiazole has proved simpler to administer than sulfapyridine, solely because it produces nausea and vomiting less frequently. Among adults, this effect is observed in 20 to 40 per cent of sulfathiazole recipients, as compared with 60 per cent or more of those who receive sulfapyridine. It is noted much less frequently in infants and children treated with either drug. Furthermore, the severity of this symptom is considerably less when sulfathiazole is used, so that therapy must be discontinued or interrupted less frequently. This may be the explanation for the lower incidence of relapses of fever and of pulmonary signs and symptoms after sulfathiazole therapy is discontinued, as compared with the incidence of these complications with sulfapyridine treatment. It may also account for the larger average amounts of drug used in the sulfathiazole-treated pneumonias. The larger dosage, however, may also be explained, in part, by the lower blood levels obtained when sulfathiazole is used in the same doses as sulfapyridine. Some physicians are consequently inclined to increase the dose of sulfathiazole in an attempt to obtain higher levels.

Sulfathiazole also has the advantage of not producing cyanosis or anemia, and it produces serious leukopenia and liver damage less often than sulfapyridine. On the other hand, drug fevers and rashes occur much more frequently with sulfathiazole. The characteristic lesions, which resemble erythema nodosum, on the extensor surfaces of the extremities, in addition to the episcleritis and the erysipeloid lesions of the face and the severe arthritis that sometimes accompanies the skin manifestations, are features of sulfathiazole toxicity not met with in sulfapyridine-treated cases.

Renal Symptoms

The most important toxic effects of sulfathiazole therapy, however, are the renal complications, which are encountered at least as frequently and probably oftener than with sulfapyridine and may be considerably more serious.[22–30] The increased danger from the renal complications of sulfathiazole therapy is related to the tendency of this chemical to precipitate, in both the free and the acetylated form, in the tubules of the kidneys, and thus to interfere with renal function either mechanically or by a direct action on the tubular epithelium. This mechanism may be operative in sulfapyridine-treated cases,[31] but is not the usual mechanism with that drug. It may account for some failures to obtain relief of sulfathiazole anuria by catheterization of the ureters and lavage of the kidney pelves and of the ureters, a method that is often successful if applied early in the anuria caused by sulfapyridine.[32–36] With sulfapyridine, the concretions of the acetylated drug are usually limited to the kidney pelvis, the ureters and the bladder. Reduced renal function in the course of continuous sulfathiazole therapy is not infrequent in animals and in clinical cases, but the function usually returns to normal after the drug is discontinued.

Because of the frequency and possible severity of the renal complications, it is essential to be on the alert for the earliest evidence of kidney damage in every patient who is treated with sulfathiazole. The urinary output must be maintained at about 1500 cc. or more daily (in adults), and the fluid intake should be adjusted accordingly. Usually, an intake of about 3000 cc. a day is necessary. Diminution in urinary output, the appearance of hematuria, retention of the drug in the blood or elevation of the blood nonprotein nitrogen is a danger sign. When one of these manifestations occurs, the drug must be stopped or the dose reduced, and the fluid intake increased. Intravenous or subcutaneous fluid in the form of physiologic saline or of 0.5 per cent glucose in water may well be used at first. Alkalies may also be helpful, and may be given as bicarbonate of soda by mouth or as a one-sixth molar solution of sodium lactate intravenously.

Trend in Pneumonia Mortality

Mention was made last year of the trend in mortality since the introduction of effective sulfonamides.[2, 37] The gross mortality for the country as a whole is difficult to evaluate because of many factors involved in the collection of such data. Some of the clinical reports, however, seem to indicate a rising case-fatality rate in chemically treated cases, even when the same drug is employed. Thus the mortality among adults in Lord's[1] collected cases treated with sulfapyridine was 6.3 per cent. Among the cases collected during the following year, the mortality was 9.8 per cent,[2] and, as noted above, the mortality was 13.7 per cent in sulfapyridine-treated cases reported during the past year by a number of workers. To

be sure, the data for the successive years are not strictly comparable, but a similar rise in the case-fatality rate has been noted in more selected groups, as, for example, in the pneumococcal pneumonias reported by a group of workers in Philadelphia. In their earliest experience with sulfapyridine, they[38] reported a mortality of 7.0 per cent in 400 cases. During the following year, they recorded a mortality of 1.50 per cent in 200 cases treated with the same drug. In that year, they had a mortality of 11.0 per cent in a parallel series of 200 cases treated with sulfathiazole. Early last season, the same group[15] reported two parallel series, each consisting of 100 cases of pneumonia, one series treated with sulfathiazole, with 17 deaths, and the other treated with sulfadiazine, with 11 deaths. If only the "typed" pneumococcal pneumonias are considered, as in their previous studies, the mortality in the sulfathiazole-treated cases was 19 per cent and in the sulfadiazine cases it was 13 per cent.[15]

A number of possible explanations of this trend may be mentioned. The first is that the severity of the disease has increased. The slight increase in the incidence of bacteremia, with the rising mortality, lends some support to this view. An increase in the occurrence of "drug-resistant" strains might account for more failures of drug therapy, but this has been proved only in rare cases. It is possible that, as the early enthusiasm accompanying a new clinical therapeutic venture wore off, stricter criteria were used in the choice of cases for inclusion in succeeding studies. This explanation likewise seems inadequate, since, if anything, the general trend has been in the opposite direction and more cases are being included for chemotherapy as experience with the drugs increases. It seems likelier that in most communities, as acquaintance with the sulfonamides diffuses among physicians, greater numbers of cases are treated by them in the home. Only the severer cases and those offering difficulties in management are sent to the clinics from which the reports emanate. Thus, in a large municipal hospital receiving primarily indigent patients, few of whom could afford treatment by private physicians, the mortality in all specifically treated cases has actually dropped in the last three successive years.[7, 39, 40]

That chemotherapy may be used successfully in the home in the great majority of cases, even among indigent patients, is shown strikingly by the work of the group of physicians at the Boston Dispensary, who are interested in domiciliary medicine.[41] Because most cases are successfully treated in the home, it is to be expected that hospital clinics and physicians engaged exclusively in consultation practice will have a higher mortality in their pneumonia cases than the internist or general practitioner in private practice.[42]

Sulfadiazine

Of the more recent sulfonamide compounds, the one that has received the most extensive trials during the past season is sulfadiazine. This chemical, which was prepared by Roblin and his associates,[43] is the pyrimidine (diazine) analogue of sulfapyridine and sulfathiazole. A preliminary report concerning this drug was made by Long[44] for the Council on Pharmacy and Chemistry of the American Medical Association, and the laboratory and clinical results obtained at the Boston City Hospital have also been published recently.[40] Although these two papers summarize most of the relevant data about sulfadiazine that are available at the time of this writing, the drug has proved to be of sufficient interest in relation to the treatment of pneumonia and other infections to warrant the inclusion here of a review of the more important information available concerning its use.

Results in Animals

Pharmacologic and therapeutic experiments with sulfadiazine were carried out in animals by Feinstone and his associates.[45] They found that this compound is less toxic than either sulfapyridine or sulfathiazole in acute experiments in mice, and that it produces less tissue damage than the latter drugs after prolonged administration in monkeys. They showed that sulfadiazine is absorbed fairly rapidly after oral administration, and that much higher levels are reached in the blood and are maintained longer than when the same doses of the other sulfonamides are used. Furthermore, the drug is found in the blood primarily in the free or unconjugated form. The acetyl derivative of sulfadiazine is excreted rapidly in the urine, where it is more soluble than the corresponding forms of sulfapyridine or sulfathiazole. Using identical dosage in mice, Feinstone found sulfadiazine to be more effective than either sulfapyridine or sulfathiazole against infections with hemolytic streptococcus, Type-1 pneumococcus and Type B Friedländer's bacillus, and about as effective as sulfathiazole against infections with staphylococcus.

Long[44] showed that in mice kept at the same blood levels, which can be maintained with considerably smaller doses of sulfadiazine than of the other sulfonamides, this drug is somewhat less effective than sulfanilamide against hemolytic

streptococcus and also slightly less effective than sulfapyridine or sulfathiazole in Type-1 pneumococcus infections, but is equal if not superior to sulfathiazole against staphylococcal infections. He also noted that sulfadiazine, when administered orally or locally, is more effective than sulfapyridine or sulfathiazole in experimental infections produced in mice by the intramuscular injection of *Clostridium welchii* and *Cl. oedematis maligni*, but that none of the drugs have any effect against *Cl. oedematis* infections. Klinefelter[46] found that sulfadiazine is also more effective than sulfathiazole against *Escherichia coli* infections in mice. He maintained approximately the same blood levels with about one tenth as much sulfadiazine.

Results in Vitro

Studies on the effect of sulfadiazine on the growth of various bacteria in vitro[40, 46–50] have been inconsistent and somewhat misleading, since they have not always paralleled the effects observed in clinical and experimental infections. Against most of the organisms tested, it has been found to be about as effective as sulfathiazole, but against others it appears to be much less effective. The discrepancies may be accounted for by the methods used. In particular, they may be associated with differences in the mediums used for the tests, some of which may exert a selectively greater inhibiting effect on some drugs than on others. This has been shown to be true in test-tube experiments with pneumococcus.[47]

Absorption and Excretion in Man

The absorption, excretion and distribution of sulfadiazine in human subjects with normal renal function have been studied by several workers.[44, 51–54] As in animals, higher concentrations are reached in the blood and are maintained for longer periods than with the same dose of any of the other commonly used sulfonamides, namely, sulfanilamide, sulfapyridine and sulfathiazole. Absorption from oral administration may be somewhat slower than with the latter compounds. Very little of the acetylated derivative is found in the blood. Up to 80 per cent of the ingested drug is excreted into the urine, and about one third of the drug recovered from this source is in the conjugated (acetylated) form. The drug diffuses rather slowly into the cerebrospinal fluid, requiring about eight to twelve hours to reach an equilibrium with the blood. On continuous therapy, the concentration in spinal fluid is usually about 80 per cent of the blood level, but may range from 50 to over 90 per cent. In pleural and ascitic fluids, the levels are essentially the same as in the blood. Sulfadiazine, like sulfapyridine and sulfathiazole, is only very slightly absorbed after rectal administration, even when the sodium salt is used. Like sulfathiazole, and in contrast to sulfapyridine and sulfanilamide, sulfadiazine is found in much lower concentration in the red blood cells than in the surrounding plasma.

Parenteral Administration

The sodium salt of sulfadiazine has been used parenterally in the same manner as the corresponding salt of sulfapyridine and sulfathiazole. It has been given intravenously as a 5 per cent solution in distilled water, or in concentrations of 0.5 to 2.0 per cent in physiologic saline solution, and has also been injected subcutaneously and intrathecally in 0.5 per cent solution in physiologic saline solution, without untoward effects.

Clinical Results in Pneumonia and Other Infections

Published clinical data are still comparatively meager and, for the most part, are given only in preliminary form. In the two parallel series of 100 pneumonia cases referred to previously, the effectiveness of sulfadiazine compared favorably with that of sulfathiazole, with respect both to mortality and to the rapidity with which the temperature fell in the recovered cases.[8] Long,[44] in his early experience, found that "sulfadiazine is slightly less effective than sulfapyridine or sulfathiazole in the treatment of pneumococcic pneumonia in human beings and that it is of definite value in the treatment of hemolytic streptococcus and staphylococcic infections in man." Plummer[55] noted that, in a small series of pneumococcal pneumonias, the clinical results compared favorably with those obtained with sulfapyridine and sulfathiazole, and that in certain other infections, particularly those due to Friedländer's bacillus, the results were encouraging. In another paper, he[9] included 51 patients with pneumococcal pneumonia treated with sulfadiazine, with 9 deaths, or a mortality rate of 18 per cent, as compared with 69 deaths, or a rate of 12 per cent, among 556 others treated with sulfapyridine, sulfathiazole or their congeners. Serum was used, in addition, in some of the cases treated with each of the drugs.

The 446 sulfadiazine-treated cases reported from the Boston City Hospital[40] included a variety of infections. Among them were 178 patients with pneumococcal pneumonia, of whom 19, or 11 per cent, died. This is the lowest mortality in any comparable group of cases previously reported from this clinic. The drug was also effective in pneumonias due to hemolytic streptococcus and

staphylococcus, in meningococcal infections, in acute infections of the upper respiratory tract, including sinusitis, in erysipelas, in acute urinary-tract infections, particularly those due to the colon bacillus, and in acute gonococcal arthritis. So far as could be judged from the small numbers of cases, sulfadiazine appeared to be as effective as sulfapyridine or sulfathiazole in each of these conditions. Dingle, Thomas and Morton[56] also found sulfadiazine to be highly effective in the treatment of a small series of cases of meningococcal meningitis, including both the epidemic and the endemic forms.

Toxic Effects

All the reports indicate that toxic manifestations from sulfadiazine are encountered much less frequently than with any of the other common sulfonamides. The toxic effects that were noted among the 872 cases reported by various authors[15, 40, 44, 53, 55, 56] may be summarized briefly. Nausea and vomiting occurred in 9.4 per cent of the cases, dermatitis in 1.7 per cent, fever alone in 0.4 per cent, hematuria in 1.0 per cent, headache or vertigo in 0.6 per cent, and leukopenia in 1.8 per cent. Crystals were found in the urine in 11.7 per cent of the cases. The following manifestations were each mentioned by only one author and were not noted by the others: scleral and conjunctival injection was noted in 2 of Long's[44] 125 cases, and a questionable psychosis was noted in 7 of Flippin's[15] 100 cases. Nitrogen retention in the blood occurred in 1.1 per cent of our cases,[40] and one case of anuria, relieved by ureteral catheterization, was included. Another case of anuria, unrelieved by catheterization and ending fatally, has been observed more recently.

Long[44, 57] has noted that, even in the face of grave kidney damage, the free and conjugated fractions of sulfadiazine seem to be more readily excreted by the damaged kidney than is usually the case with sulfapyridine and sulfathiazole, and this corresponds with our experience.[40] Anemia and cyanosis have not been observed in any of the cases. With respect to the cyanosis, it has been shown that carbonic anhydrase is not inhibited by sulfadiazine or by sulfathiazole, but it is inhibited by sulfanilamide, which caused this symptom so frequently.[58]

Dosage

In general, sulfadiazine has been used in the same doses as the other sulfonamides. It is given orally whenever possible. The initial dose for adults is 4 gm., and this is followed by 1 gm. every four hours until the temperature reaches normal; some prefer to continue this dose for one or two days longer. It is then reduced to 1 gm. every six hours. Blood levels between 7 and 10 mg. per 100 cc. are maintained readily on this schedule in most patients who are on an adequate fluid intake (2500 to 3000 cc. daily). In patients who are comatose or vomiting severely, and in others who are extremely ill, it may be of advantage to give an initial dose of 5 gm. of the sodium salt parenterally in the manner already mentioned. Follow-up doses of 2 or 3 gm. of the sodium salt may then be given at intervals of eight to twelve hours, preferably subcutaneously in 400 or 600 cc. (0.5 per cent) of physiologic saline solution, but a shift to the oral route should be made as soon as possible.

Failures and Secondary Fevers in Sulfonamide-Treated Cases of Pneumococcal Pneumonia

The factors influencing mortality have recently been analyzed in a group of 800 cases of adult pneumococcal pneumonia treated with sulfapyridine and sulfathiazole.[59] The most important factors were age and bacteremia. The mortality in the patients over forty years of age was 15.4 per cent, a rate almost four and a half times as great as that in those less than forty years old (3.5 per cent). The bacteremic patients had a mortality rate of 32.3 per cent, which was nearly five times as high as that in the patients with negative blood cultures (6.8 per cent). Late treatment was also an important factor. When treatment was started on the fifth day or later, the mortality (18.4 per cent) was almost three times as high as that in the patients in whom treatment was begun on the fourth day or earlier (5.6 per cent). The type of pneumococcus was also important. The death rate in the Type-3 cases was 20 per cent, as compared with 10.5 and 7.0 per cent in Type-1 and Type-2 cases, respectively, and 8.0 per cent in those due to other types. Complications of the pneumonia influenced the mortality appreciably, but much less than the presence of other associated severe diseases. The most frequent of the latter were heart disease and alcoholism. The mortality in the cardiac patients was 31.3 per cent, and among the alcoholics, 20.5 per cent. Sex and color had no appreciable effect on the mortality in these cases.

These findings are in essential agreement with the results of all other analyses of mortality in cases of pneumococcal pneumonia that have been recorded in the past. The same factors are equally important in patients treated symptomatically without the aid of specific measures, as well as in patients treated specifically with serums or chemicals, or both. It is not to be inferred, however, that old patients, those with bacteremia or with Type-3

pneumococcus infections and those with associated diseases, are not benefited by the therapy. The prognosis for recovery without specific treatment is very poor in such cases, but the reduction in death rate and the improvement in the clinical course resulting from chemotherapy are almost of the same order as among other cases.[60] This was clearly demonstrated recently for the old-age pneumonias. In one group of such cases, the mortality was reduced from an average of 75.0 per cent to 23.5 per cent by the use of sulfapyridine, and the average duration of fever was reduced from twelve to three days by chemotherapy.[61]

The causes of secondary fever among 339 sulfapyridine-treated cases of pneumococcal pneumonia were reviewed recently by Dowling and Abernethy.[62] Relapses of fever and symptoms of pneumonia occurred in 15 cases after apparent temporary improvement, but before the signs and symptoms had entirely cleared. In 7 of these cases, the dose seemed to be adequate, as judged by the high levels of the drug in the blood. Five of the cases, including 4 of the latter, were Type-3 pneumococcus pneumonias, and 3 of the 4 deaths among these 15 cases were in patients with this type. It is of interest in this connection that Type-3 strains have been found to respond less regularly to sulfapyridine therapy than Type-1 or Type-2 strains in experimental infections in mice.[63]

So-called "drug fever" occurred in 7 cases reported by Dowling and Abernethy. This diagnosis was based on the concomitant presence of a morbilliform rash in 3 cases, and on high fever, without signs of marked toxicity or in the absence of other demonstrable cause of fever, in the remaining cases. The drug fever began from two to four and one-half days after the crisis and continued for one and one-half to four days, regardless of whether administration of the drug was continued or stopped. All these patients recovered.

In 6 of Dowling and Abernethy's patients, a second attack of pneumonia caused by a different type of pneumococcus occurred while treatment with sulfapyridine was being continued and after apparent recovery from the original attack. All these patients recovered from the recurrence. Serum was used, in addition to sulfapyridine, in the first attack in 2 cases, and sulfapyridine was used alone in all the other attacks, except in 2 of the recurrences, in which only symptomatic treatment was given. Such recurrences have not been encountered previously by these authors in any of 65 patients who were treated symptomatically, and occurred in only 1 out of 120 cases treated with serum alone.

The fourth cause of secondary fever, according to Dowling and Abernethy, was the occurrence of complications of the pneumonia. This accounted for 4 cases.

In the experiences with sulfathiazole referred to earlier, relapses and recurrences have been much less frequent than with sulfapyridine. On the other hand, drug fevers and rashes were considerably more frequent. Sulfathiazole fevers, with or without dermatitis, may be associated with severe symptoms, including chills, so that a relapse of infection or the occurrence of complications or of other intercurrent infections is suspected, but the pulmonary symptoms do not recur. It has been our experience that sulfathiazole fever, especially when accompanied by a rash, usually progresses under continued treatment and only rarely subsides before the drug is withdrawn.

Chemotherapy in Nonpneumococcal Pneumonias

Most of the reports dealing with the chemotherapy of pneumonia and containing bacteriologic data have dealt primarily with pneumococcal pneumonias. Occasional cases of primary pneumonia due to other organisms are included. Sulfonamides have been used in such cases because of the known effectiveness of the drugs in other infections with the same organisms or because no other effective remedy is available. It is therefore difficult to assess the value of chemotherapy under such conditions. A few recent reports have dealt primarily with nonpneumococcal pneumonias and may be reviewed briefly.

Streptococcal Pneumonia

Lawrence and Sutliff[64] have recently summarized part of the experience of the New York City pneumonia-control program with respect to the role of hemolytic streptococci in pneumonia. During the winter of their study, 5.05 per cent of all sputum specimens examined in the health-department laboratory yielded cultures in which more than 15 per cent of the colonies were hemolytic streptococci. In 15 of 141 patients from whom these specimens were obtained, there was no pneumonia. In 45 of the others, the streptococci were associated with pneumococci, and in the remaining 81 cases of pneumonia the streptococcus was the only significant organism.

The fatality rate for their entire series of 126 cases was 10.3 per cent. Only 22 of the cases were hospitalized, and 7 of the 13 patients who died were hospitalized. This makes a fatality rate of 6 per cent in the home-treated cases and 32 per cent in the hospitalized patients. Empyema occurred in only 3 per cent of all the cases and

in 18 per cent of those treated in hospitals. In 10 cases receiving adequate doses of sulfanilamide, there were no deaths; among 57 cases receiving less than the generally recommended doses of sulfanilamide, 8 deaths were reported, a fatality rate of 14 per cent; and of 59 patients who received no sulfanilamide, 4 died, a rate of 8 per cent.

Keefer, Rantz and Rammelkamp[65] studied 55 cases of hemolytic streptococcus pneumonia and empyema treated with sulfanilamide and sulfapyridine. There were 39 cases of pneumonia alone, and 14 of the other 16 cases had empyema, which followed an infection of the lung. The mortality rate in all the cases was 18 per cent, and it was the same whether or not empyema was present. Bacteremia occurred in 7 patients, of whom 4 died. In these cases, the use of sulfanilamide or sulfapyridine did not reduce the incidence of empyema, nor did it shorten the course of the disease. There was suggestive evidence that the fatality rate in both the cases of pneumonia and empyema was reduced by using these drugs. Four patients with empyema recovered following multiple aspirations of the chest, and chemotherapy. The best results, however, were obtained with a combination of chemotherapy and thoracotomy.

Carey[20] used sulfapyridine in the treatment of 42 infants and children with hemolytic streptococcus pneumonia, and also treated 21 such patients with sulfathiazole. The death rate in patients under two years of age was 26 per cent, and in those over two years old it was 6 per cent. After those who died within twenty-four hours were excluded, the death rate was 3 per cent in each group. There was no significant difference in the average duration of the disease after treatment with the two drugs used.

Sulfadiazine has proved highly effective in the few cases of hemolytic streptococcus pneumonia in adults in which it has been used.[40, 49] Of the 4 cases included in our report,[40] 2 had bacteremia and 2, including 1 of the latter, had empyema. All 4 patients recovered completely without operation.

Staphylococcal Pneumonia

Although numerous reports are available of sulfonamide-treated cases of staphylococcal infections, particularly cases of staphylococcal sepsis treated with sulfathiazole, data concerning the effects of the drugs in primary pneumonias due to *Staphylococcus aureus* are very scant. Individual cases or groups of a few such cases are scattered among some of the reports dealing with the chemotherapy of pneumonia or of staphylococcal infections. On the whole, the results of treatment with sulfanilamide or sulfapyridine have not been favorable except, perhaps, in individual cases. On the other hand, the results of sulfathiazole therapy have been encouraging.

Carey[20] included 15 cases of staphylococcal pneumonia in his series. The fatality rate was 50 per cent in infants under two years of age, if the patients dying within twenty-four hours of admission to the hospital are included. Sulfapyridine was used in 8 of the patients, all of whom died, whereas 5 of the 7 sulfathiazole-treated patients recovered. One of the sulfathiazole-treated patients died ten hours after entry to the hospital, whereas the other died after seven days of intensive treatment with this drug. Shulman[66] has recently reported 2 severe cases of staphylococcal tracheobronchitis in infants successfully treated with sulfamethylthiazole and sulfathiazole.

Our report on sulfadiazine therapy[40] included 29 cases of staphylococcal pneumonia. Positive blood cultures for *Staph. aureus* were obtained from 3 of the patients, all of whom recovered. In addition to the staphylococcus, influenza bacilli were cultivated from 3 cases and hemolytic streptococci from 5, including a patient in whom the latter organism invaded the blood stream. There were 6 deaths (21 per cent) among the 29 cases, including the one with hemolytic streptococcus bacteremia. Fluid was obtained by thoracentesis in 6 of the patients who recovered. The original fluid and subsequent ones were all sterile in 2 of these cases. In the remaining 4, the original fluid was infected with staphylococci; 2 of these patients recovered completely following sulfadiazine therapy and thoracenteses, and the other 2 were drained by thoracotomy. A number of cases of staphylococcal pneumonia occurred during the past winter as complications of epidemic influenza, which was prevalent at that time. Except for some fulminating cases, these patients responded well to either sulfathiazole or sulfadiazine, although the course was frequently prolonged or associated with empyema or with abscess formation in the lungs.[67]

Friedländer Pneumonia

The mortality in acute primary Friedländer pneumonia treated without specific agents is very high. Only 1 patient in 32 cases reported by Solomon[68] recovered, and all of 5 treated with serum died. In Bullowa's[69] first series, there were 7 recoveries among 41 cases, a mortality of 83 per cent. Among the 24 cases in his series that were due to the Type A Friedländer bacillus, 6 patients received type-specific serum, and 3 recov-

ered, whereas only 1 recovered among the 18 who were treated without specific serum. More recently, Solomon[70] reported a group of 17 cases of chronic Friedländer bacillus pneumonia. Sulfapyridine was used in 4 of these patients, all of whom recovered, although pulmonary suppuration continued without apparent effect. One of these patients had a positive blood culture. Another bacteremic patient was treated with sulfanilamide and recovered, although he, too, contracted lung abscesses. Among the 12 patients treated without sulfonamide drugs, there were 4 deaths, but 2 of those who recovered had positive blood cultures. More recently, Perlman and Bullowa[71] presented a second series of 37 cases of primary Friedländer pneumonia, with a mortality of 84 per cent. Among these patients, 9 were treated with sulfanilamide or sulfapyridine, and 6 died; 7 received these sulfonamides in addition to specific serum, and only 1 recovered; 13 with Type-A infection received specific serum alone, and all died; and of 8 who were given only symptomatic treatment, 2 recovered.

These reports indicate that treatment with sulfanilamide or sulfapyridine may be successful in individual cases, but the results as a whole are not very favorable. Reports of sulfathiazole-treated cases are still too few to evaluate. However, the greater effectiveness of sulfadiazine in experimental Friedländer-bacillus infections[45] suggests that one may look forward to better results from this drug.

Pneumonias of Undetermined Etiology

Recent reports concerning chemotherapy in pneumonia include a considerable number of cases in which the bacteriologic studies fail to yield pneumococci or other organisms that might be considered etiologic. In many of these cases, the predominant organism obtained from direct cultures of the sputum is either *Streptococcus viridans* or a nonhemolytic or slightly hemolytic (alpha) streptococcus. The relation of such streptococci to the disease is difficult to evaluate, although in rare cases they seem to be significant, since they are also obtained in cultures of the blood or of pleural exudate and are frequently cultivated from the lungs at autopsy. Some of these cases have all the clinical features of typical lobar pneumonia, whereas others have atypical lesions and symptoms. Most of these patients apparently respond well to sulfonamides. Among 52 cases treated with sulfadiazine, there were 3 deaths, and all the fatal cases were in patients over sixty years old who had atypical pneumonias.[40] It is possible that many of the cases in this category, particularly those with typical lobar pneumonia that respond so well to chemotherapy, are cases of mild pneumococcal pneumonia in which the causative organism escapes detection. Other cases of atypical pneumonia in which the patients fail to show any clinical response but nevertheless eventually recover may be due to viruses as yet unidentified.

Attention was called recently to a group of atypical pulmonary infections complicating severe and intractable bronchial asthma or congestive cardiac failure. The bacteriology in these cases is often unrevealing. Proper treatment of these cases with sulfathiazole or sulfadiazine may not only result in prompt improvement in the pulmonary infection, but may also render the underlying condition more amenable to appropriate treatment.[72]

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27311

PRESENTATION OF CASE

A thirty-year-old housewife entered the hospital complaining of generalized aches and pains.

The patient felt well until five years before admission, when a rather severe, sharp pain developed in her left knee; this was aggravated by motion. Six months later, a tender swelling appeared above this joint; and the pain extended to her left hip and lower back, and another swelling developed in the right tibia. Approximately one year after the onset of her symptoms, several bone cysts were said to have been removed from her jaw. Three years before entry, and without untoward symptoms, the patient gave birth to a normal child by forceps delivery; during her confinement she suffered from severe pyorrhea. Shortly afterward, the back pain became severer and spread to the thoracic spine, sternum, left shoulder and lower left ribs, where another tender swelling developed. At that time the patient entered an outside hospital, where her complaints were generalized aches and pains, polyuria and polydipsia. Examination revealed bilateral exophthalmos and small painless swellings over the mandible and tibia. X-ray study showed areas of decreased density in the skull and jaws, with a large cystic growth in the right tibia. An intravenous pyelogram demonstrated a calculus in the left ureter, with no dye from the right kidney. The blood calcium was 13 mg., the phosphorus 2.8 mg. per 100 cc. and the basal metabolic rate +9 per cent. A bilateral cervical exploration for a parathyroid tumor was performed without success. Two weeks later, an air injection into the mediastinum revealed no tumor, and subsequent exploration of the anterior mediastinum was fruitless. The patient was discharged from the hospital for a rest period, with a view to re-exploration. Several weeks later, however, she visited her own physician and complained of nervousness. A thyroidectomy was thereupon performed, but the apparent benefit derived from this procedure was short lived and her aches and pains returned, with pronounced tenderness over the tumor sites.

During the period between two years and one year before admission, the patient suffered from severe headaches, most marked in the right temporal region, with tenderness in the entire calvarium; and for the previous eight months she had been forced to remain in bed, not from weakness, but because of pain.

Six months before admission, the patient entered a clinic, where another parathyroid exploration was unsuccessful.

At the time of admission to this hospital, in addition to her other symptoms, she complained of chest pain aggravated by deep breathing and coughing. There had been no loss in weight. A frequency of urination, with a nocturia of one to three times, had been present for about five years.

The family history was irrelevant. The patient had had the usual childhood diseases. She was in the habit of drinking a quart of milk each day.

On examination, the patient exhibited a yellowish pallor and was chronically ill, but in no obvious distress except on moving or being moved, when pain was apparent. There was exophthalmos, and the skin was dry, with slight hirsutism of the face and chest. The nose and throat were normal. There were numerous irregular, tender swellings over the scalp, mandible, seventh cervical spine, left clavicle, left lower-chest wall in the midaxillary line, both tibias at their upper ends and the middle of the left femur. Moderate tenderness on pressure was present over both crests of the ilium, more marked on the left. The heart was slightly enlarged, with a blowing systolic murmur best heard in the pulmonic area and along the left sternal border; the blood pressure was 110 systolic, 70 diastolic. The lungs were normal. There was moderate tenderness, without spasm, in both lower quadrants of the abdomen. Pelvic examination was negative.

Examination of the urine showed a specific gravity between 1.008 and 1.028, with ++ to ++++ tests for albumin. The sediment was often "loaded" with white blood cells and occasionally with red blood cells. A phenolsulfonephthalein test showed 5 per cent excretion in fifteen minutes and a total of 20 per cent in half an hour. Repeated, there was a 15 per cent excretion in thirty minutes and a total of 25 per cent in an hour. Numerous Sulkowitch tests for urinary calcium varied from + to +++.

The blood showed a red-cell count of 2,300,000 with a hemoglobin of 55 per cent, and a white-cell count between 6000 and 14,000. A stained film was normal, and the reticulocyte counts varied between 2.0 and 5.2 per cent. The sedimentation rate was 8 mm. in one hour, the prothrombin time 40 seconds (normal, 20 seconds), and the hemato-

crit reading 37.5 per cent. The nonprotein nitrogen of the blood serum was 29 mg., the cholesterol 59 to 100 mg., the calcium 14.5 mg., the phosphorus 2.1 mg., the phosphatase 11.8 Bodansky units, and the protein 6.2 gm per 100 cc. The chlorides were 110.9 milliequiv., and the carbon-dioxide combining power 22.8 milliequiv. per liter. The serum van den Bergh was 2.1 mg. per 100 cc., biphasic; a bromsulfalein test showed 50 per cent retention; and a Congo red test showed 90 per cent retention of the dye in the serum. A gastric analysis showed free acid; the stools were normal. The basal metabolic rate was +32, +19 and +24 per cent on three occasions.

X-ray films of the bones showed a large defect in the skull in the right frontoparietal region, and a smaller defect in the upper frontal region. The entire calvarium was grossly thickened, and the margins of the inner and outer tables were obliterated. The bones showed a generalized decalcification, with large cystlike areas of rarefaction in the iliums, femurs, bones of the pelvis, ribs, scapulas and humeri. There was extensive rarefaction of the upper shaft of the left humerus, with destruction of the cortex on the lateral aspect. The bones of both forearms and hands showed changes similar to those in the other bones. An area of increased density was present in the distal extremity of the left radius, and a similar area in the distal extremity of the humerus. The lesions in the ribs and the upper extremity of the left tibia and both iliums showed marked thinning of the cortex, with expansion of the bones. The left acetabulum was thin, with intrapelvic protrusion of the left side of the pelvis in the region of the acetabulum. The vertebras showed increased density in contrast to the other bones, and the trabeculations were irregular. Pathologic fractures were present in the second and the third lumbar vertebra, and the body of the fourth lumbar vertebra showed marked decalcification. The bones of the right foot showed decalcification, and there was a cystlike area in the distal extremity of the tibia.

With an intravenous pyelogram, the kidneys were obscured by gas in the intestine. There were two areas of calcification in the mid-abdomen, and one overlying the sacrum, all of which had the appearance of calcified lymph nodes. There was also a 2-cm. oval area of calcification overlying the transverse process of the fifth lumbar vertebra on the left, approximately in the course of the ureter. This shadow was somewhat denser and more smoothly rounded than the other shadows. Intravenous dye appeared on the right, and the kidney pelves and calyxes appeared normal. There was no evidence of excretion of the dye on the left.

Fluoroscopy and barium in the esophagus failed to outline a pathologic mass in the upper mediastinum. Laminograms of the anterior mediastinum failed to show evidence of disease.

X-ray films of the bones taken at another hospital three years previously showed that the osteoblastic areas present at that time in the lower radius and right tibia were typical benign giant-cell areas.

An electroencephalogram was normal.

On admission, the patient was very ill, and on the fourth hospital day a 500-cc. blood transfusion was given. At the end of a week, a biopsy was taken from the left ilium.

Differential Diagnosis

Dr. Wyman Richardson: "Three years before entry, and without untoward symptoms, the patient gave birth to a normal child by forceps delivery; during her confinement she suffered from severe pyorrhea." Just what that means, I am not sure. It may mean that pre-existing bone disease was aggravated by pregnancy and resulted in pyorrhea. ". . . another parathyroid exploration was unsuccessful." I do not know where they looked for it. I am interested in knowing whether the sternum was split.

Dr. Tracy B. Mallory: It was — on at least one occasion.

Dr. Richardson: There is no record of the temperature. I assume that it was normal.

Dr. Oliver Cope: The patient did have a little fever, but seldom more than a degree above normal.

Dr. Richardson: "X-ray films of the bones taken at another hospital three years previously showed that the osteoblastic areas present at that time in the lower radius and right tibia were typical benign giant-cell areas." Do you know what that means, Dr. Lingley, or should I ask you?

Dr. James R. Lingley: The cystic areas spontaneously filled in with new bone, which is unusual. I suspect that the patient had a fracture.

Dr. Richardson: I do not consider myself an expert on bone diseases. However, I shall try to see what I can do. There are four things that one should try to explain: bone disease, liver disease, as shown by the bromsulfalein retention; bone-marrow disturbance, as evidenced by the severe degree of anemia; and kidney disease.

I shall start with bone disease. Perhaps we might look at some of these lesions, if Dr. Lingley will be so good as to show the films. I particularly want him to tell me if the lamina dura is absent.

DR. LINGLEY: This is a generalized condition of bone characterized by multiple large cystlike areas of destruction. The process is most extensive in the pelvis, where one can see tremendous cystic areas in both iliums and intrapelvic protrusion of the acetabulum. In the spine, the decalcification involves the central portions of the vertebras more than the margins, so that the margins appear denser in contrast. Some of the vertebras show pathologic fractures. In the lower extremity of the radius, there is one area of increased density. The process is otherwise one of decalcification. The new-bone formation in this one area may have been due to a healed fracture. The process in the skull is characterized by generalized thickening of the calvarium and a large area of destruction in the frontoparietal region.

DR. RICHARDSON: The patient had teeth, and the lamina dura was absent. Is that not true?

DR. LINGLEY: Yes; and I did not mention an area of calcification in the region of the left ureter. That has the appearance of a calculus. The kidney is nonfunctioning on the left side.

DR. RICHARDSON: In regard to the bone disease, it is evident that this patient had overactive parathyroid tissue. The serum calcium was high, the phosphorus low. The phosphatase of 11.8 units seems to me to be a low figure in view of the degree of bone involvement, and that bothers me a little. However, I cannot see how you can get this picture with any widespread tumor process, and I therefore think it is a parathyroid effect. The fact that she was thoroughly explored and no adenoma found does not, I believe, rule out the possibility that one of these tumors was hidden and not found.

The next question to be considered is whether this might have been some type of secondary hyperplasia of the parathyroid glands, but I cannot see any good reason for such secondary hyperplasia and I have to rule it out. Therefore, I should say that this patient had primary hyperparathyroidism, probably due to a parathyroid adenoma, and that one should continue looking for it.

There are other things that are more difficult for me to explain. She had a marked anemia, apparently of a macrocytic type, with some evidence of reticulocyte increase. If one were to look at the blood smear, one would probably find evidence of bone-marrow activity. I do not recall an anemia of that type associated with parathyroid disease, and it seems to suggest that there is more evidence of encroachment on the bone marrow than would be explained by cystic changes such as she showed. I do not see why disease of the bone of this type should interfere with marrow function to this extent, and I am bothered by that. I shall go back to it in a minute.

In regard to the liver, the serum van den Bergh was slightly above normal, and there was 50 per cent retention of bromsulfalein, so that there is evidence of some disturbance of hepatic function. We know this patient had a renal stone, presumably because she had been excreting so much calcium. One kidney is said not to have excreted any dye. On the other hand, excretion of phenolsulfonephthalein dye was fairly good, considering the renal function as a whole — 20 per cent in half an hour, and 25 per cent in another test; function was definitely impaired, but not markedly so. The urine could be concentrated up to 1.028. At the same time, the patient had marked albuminuria, and the blood pressure was 110 systolic, 70 diastolic. There was no hypertension. She was entitled, of course, to some kidney infection along with the stone. It seems to me that the renal picture, with that degree of albuminuria, with normal blood pressure and with normal nonprotein nitrogen, is the picture one sees with nephrosis. If one considers that as a possibility, one begins to wonder whether there was some other condition that involved the kidney, the liver and the bone marrow. A Congo red test gave 90 per cent retention of the dye. If one considers it specific for amyloid disease, one would have to say that for some reason this patient had amyloid disease. Usually, of course, amyloid disease is associated with infection, and I cannot make out that this patient could have had a long-standing infection. I do not see any reason to consider amyloid disease.

DR. COPE: I should have spoken up sooner. Ninety per cent of the dye was still found within the serum. We considered it normal.

DR. RICHARDSON: The Congo red test, then, is against amyloid disease, and it is foolish to talk about it anyway. As a matter of fact, I do not consider the Congo red test to be worth anything. It may possibly be valuable when 90 per cent, or so, of the dye is taken up. However, since I can think of no other explanation of hepatic involvement, I raise a question of amyloid disease.

I shall leave my discussion there and say that this patient had primary hyperparathyroidism probably due to adenoma, with secondary renal calculus and bone changes.

DR. J. H. MEANS: I should like to know more about the thyroid situation. There is just enough given here to be tantalizing, but hardly illuminat-

ing. It is a mystery why they took out the thyroid gland, why the patient had exophthalmos, and why the metabolic rate went up rather than down after thyroidectomy.

DR. RICHARDSON: I meant to mention the exophthalmos. I wonder if she had always been a little exophthalmic; and if not, could it not have been due to some lesion in the orbit?

DR. FULLER ALBRIGHT: She had an unusually thick skull.

DR. LINGLEY: There is thickening of the bones all around the orbits. I do not see any reason why that might not be the cause of the exophthalmos.

DR. RICHARDSON: As for the basal metabolic rate, I wonder whether it was basal. She had a severe anemia and a fever.

DR. ALBRIGHT: I believe they took out the thyroid gland in looking for the parathyroid tumor. They thought it might be in the thyroid gland.

A PHYSICIAN: How do you explain the continuous severe headaches?

DR. RICHARDSON: There was enough bone disease to account for that. Is it true that people with high blood-calcium levels have headaches?

DR. ALBRIGHT: I do not believe so.

A PHYSICIAN: Was a lumbar puncture ever done?

DR. COPE: She could not be rolled over. It was very difficult even to take x-ray pictures. She was very ill, and the plates were taken one or two at a time.

DR. WILLIAM B. BREED: Could the large skull lesion account for the headaches?

DR. ALBRIGHT: Yes; it most certainly could. There is a huge blood supply to this type of lesion.

We came to the same conclusion as Dr. Richardson, with exactly the same misgivings. There were four reasons why we were puzzled. In the first place, the patient had been operated on at two excellent clinics and no tumor had been found. That is only a fairly good reason. Secondly, the skeletal x-ray films showed localized areas of normal bone density. One can have a patient with hyperparathyroidism and no bone disease, but if there is bone disease it should be generalized. Dr. Cope finally explained these areas by going back to previous x-ray films and finding that there had been cysts in these same areas. Thirdly, we were also disturbed about the phosphatase. It was high, but not so high as we should have expected for the degree of bone disease. But the thing that disturbed us most of all was the anemia. When one meets bone disease with anemia, one worries, of course, about some bone-marrow tumor. However, a bright thought was finally brought forth to explain the anemia. After all, this patient was a mass of giant-cell tumors. These are very vascular lesions and have many hemorrhages into them. This gives them their characteristic brown color, which is due to changed hemoglobin. We, therefore, finally concluded that her anemia was due to blood loss into her bones.

DR. RICHARDSON: The anemia as described could not be due to chronic blood loss.

DR. ALBRIGHT: I wonder if the figure for the hematocrit is correct.

DR. MALLORY: There are two figures recorded here — a hematocrit of 20 per cent, corresponding to a red-cell count of 2,300,000, and one of 37.5 per cent, going with a red-cell count of 3,400,000. The second pair of figures followed several transfusions.

DR. RICHARDSON: The hematocrit was approximately normal then, whereas an anemia due to blood loss should be definitely microcytic and hypochromic. Is there a description of the blood smear?

DR. ALBRIGHT: Dr. Bernard M. Jacobson reported normocytic, normochromic red cells and no immature red or white cells except for the reticulocytes, which were always high varying from 2 to 5 per cent. The serum van den Bergh was a little high, 2.0 mg., and the urobilinogen was increased, a finding suggesting increased blood destruction.

DR. RICHARDSON: The blood picture as reported by Dr. Jacobson is nonspecific, and without examining the smear myself I hesitate to make further comment.

DR. COPE: Dr. Albright comforted me a great deal by being worried, because we certainly were worried. It is fair to emphasize that, in addition to the increased bone density in the three areas, the patient had four huge giant-cell tumors of a size that we have not encountered in any other patient with hyperparathyroidism. It occurred to us that perhaps she had malignant bone disease originating in the giant-cell tumors, and I hope that Dr. Mallory will discuss this, because roughly 7 per cent of the benign giant-cell tumors of adolescence become malignant. We have not, curiously enough, encountered the development of bone malignancy in any of the areas of microscopically similar giant-cell tumors in hyperparathyroidism. Patients with hyperparathyroidism may have hundreds of these tumors.

In the x-ray films, the large tumor areas appear to be cystic. When we cut down on the one in the ilium, it was a huge solid tumor like a very stiff sponge, very vascular, with a thin cortex of bone. We were interested to know

whether it was malignant. Why should the one area in the skull have outgrown all the other areas? If this was hyperparathyroidism, the small defects must have been multiple small giant-cell areas. We could not explain either the localized overgrowth or the anemia.

It is again fair to emphasize, from the point of view of diagnosis, that this patient had been operated on four times, twice by a professor in one of our leading medical schools and two other times by men skilled in thyroid surgery. A mistake in diagnosis can easily be made because a malignant lesion spreading rapidly in bone can reproduce the abnormal metabolic and blood findings of hyperparathyroidism.

Dr. Mallory: I might put a word in here. The first operation here was a biopsy of the crest of the ilium, and the specimen showed a so-called "brown tumor," microscopically indistinguishable from a benign giant-cell tumor, but in the bone surrounding that tumor was very obvious osteitis fibrosa cystica, so that our opinion that this was hyperparathyroidism was distinctly strengthened.

Dr. Albright: Was there any hemosiderin?

Dr. Mallory: It was obvious in all the sections. However, one may see a good deal of hemosiderin in giant-cell tumors of the spontaneous variety. Following the biopsy, the patient was again explored by Dr. Cope in search of a parathyroid tumor.

Clinical Diagnosis

Hyperparathyroidism.

Dr. Richardson's Diagnosis

Parathyroid adenoma.
(Amyloid disease ?)

Anatomical Diagnoses

Parathyroid adenoma.
Osteitis fibrosa cystica.

Pathological Discussion

Dr. Cope: Once convinced that this patient must have had a parathyroid tumor, we laid a plan of attack, suspecting that the previous incision in the sternum had not been long enough. We opened the chest, dividing the sternum down the mid-line and intending to go low, but then we came to the inferior end of the thymus in front of the aorta. I changed my plan of attack immediately, because it was unlikely that the parathyroid adenoma would lie lower than the lower border of the thymus; therefore, in spite of the scar tissues, we dissected upward, following the thymus as a guide. If an adenoma of the parathyroid exists in a chest, it must have come down embryologically with thymus tissue, being the so-called "parathymus gland." The adenoma lay not within the thymic substance but behind it, displaced posteriorly and actually into the middle mediastinum.

Dr. Mallory: The other questions that Dr. Richardson raised we have no answer to. The tumor was an obvious adenoma of fairly good size, as one might expect. We cannot answer any questions about possible liver disease or the state of the kidneys. There was no evidence of amyloid disease in the tissues that we saw. That does not rule it out, however. So far as speculation regarding anemia is concerned, I should be inclined to vote for the myelophthisic origin. One can see from the x-ray films that a large proportion of the disease is in the flat bones and vertebral column, which are the areas where most blood is formed.

A Physician: What happened to the patient later?

Dr. Cope: It was a dramatic case. The operation was performed less than three months ago. The patient is already sitting up, but not quite ready to walk. The anemia is interesting. Within a week, the reticulocytes had disappeared from the blood, only to return later. We have no explanation for this. She had been living on transfusions since June, 1940. She has had none since operation, and her anemia slowly decreased.

Dr. Mallory: Are you going to do anything about the kidney stone, or are you content to leave well enough alone?

Dr. Cope: The kidney stone was seen three years ago at the time of the first parathyroid exploration. It was in the identical position, and there was no function of the kidney at that time. The only change is that the stone, which has a half-moon curve, has turned over. I wish Dr. Smith would say something about that.

The patient has become afebrile, which is another curious thing. The chart showed an abrupt drop after operation, so that the fever before operation did not seem to be due to infection because there was no reason why the operation should have rid her of infection. I thought that preoperatively the left kidney might have been infected, but the preoperative course certainly suggests that that is not true.

Dr. Mallory: What do you believe should be done, Dr. Smith?

Dr. George G. Smith: I should leave the stone alone.

Dr. Richardson: I have one other theory about the anemia. The patient had been sick for a long

time and eating very little. The question is whether a quart of milk a day would be sufficient to produce the necessary extrinsic factor for blood formation. It might be a macrocytic anemia due to the lack of the food factor described by Castle.*

DR. ALBRIGHT: But she had reticulocyte response.

DR. RICHARDSON: That is the feature of myelophthisic anemia. Such patients have reticulocytes, nucleated red cells, polychromatophilia and so forth.

DR. ALBRIGHT: I shall have to read my book again.

CASE 27312

PRESENTATION OF CASE

A fifty-three-year-old woman entered the hospital complaining of "dizzy spells."

The patient felt well until the birth of her last child, sixteen years before admission. Ever since that time, she had suffered from attacks of weakness and palpitation and from a sensation of fainting. The attacks lasted ten to fifteen minutes, came on in any position and at any time, and were relieved by lying down. One year after the onset, the patient was admitted to a hospital for three months, where a diagnosis of cancer was made and x-ray treatments were given to her left chest. This resulted in complete relief for the next five years, at the end of which time the attacks reappeared. Sixteen x-ray treatments were directed at the same region in her chest, and again there was relief and she was "able to breathe better." The patient then felt well until eight months before admission, when the "spells" recurred. She consulted her physician, who said that her "left chest had filled up again," and subsequently sixteen x-ray treatments were given. This time, there was no relief, and operation was advised. At no time had there been pain, cough, hemoptysis, dyspnea, orthopnea, edema, nausea, vomiting, tarry stools or loss of weight.

The family history and past illnesses were irrelevant.

On examination, the patient was well developed and well nourished and in no distress. The left border of the heart could not be made out, but the organ was displaced to the right. There were no murmurs, and the rhythm was irregular, without pulse deficit; the blood pressure was 140 systolic, 84 diastolic. Examination of the lungs showed dullness to percussion, absent tactile and vocal fremitus, and absent breath sounds over the entire left chest anteriorly from the level of the first rib down and posteriorly from the level of the third dorsal vertebra.

Examination of the abdomen and nervous system was negative.

The temperature was normal, the pulse 94, and the respirations 23.

The urine gave a + test for albumin. The blood showed a red-cell count of 4,340,000 with a hemoglobin of 13.0 gm (photoelectric-cell technic), and a white-cell count of 16,600. A blood Hinton reaction was negative.

An x-ray film of the chest showed an unusually large mass occupying the lower three fourths of the left side of the chest and displacing the heart shadow to the right. The upper margin of the mass was sharply defined and smoothly rounded, without lobulations, and the greater portion of the tumor lay anteriorly. It was homogeneous in density, and no areas of calcification were seen within it. The right lung field was clear.

A barium swallow showed the esophagus to be displaced to the right along with the heart shadow. The mass itself, however, did not appear to extend as far medially as the esophagus.

On the seventh hospital day, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. RICHARD H. SWEET: There were no symptoms referable to her chest; hence, we are dealing with a mediastinal tumor, and I presume that much of the differential diagnosis depends on the examination of the x-ray films. May we see them, Dr. Hampton?

DR. AUBREY O. HAMPTON: All these films were taken within three days, so that we had no time control. The mass does lie anteriorly. Although you probably cannot see it from your seats, this is the posterior margin, very sharp and smooth. Variation in position of the patient did not seem to change the shape of the mass. It remains at about the same level in all the films. It does not seem to move with respiration. The esophagus is displaced, and the visible portions of the lungs are perfectly normal. There is no evidence of disease in the ribs or spine. We cannot see the anterior ends of the ribs very well, and a mass lying anteriorly might involve them without showing. I do not believe that is the case here. The ribs are thin, as they often are in this area, but they are not separated.

DR. SWEET: The history is puzzling because of its long duration and because of the statements

*Castle, W. B., Townsend, W. C., and Heath, C. W. Observations on the etiologic relationship of achylia gastrica to pernicious anemia. III. The nature of the reaction between normal human gastric juice and beef muscle leading to clinical improvement and increased blood formation similar to the effect of liver feeding. *Am. J. M. Sc.* **180**:305-335, 1930.

made about the benefits obtained from x-ray treatment. I cannot believe that the patient had anything that should have been treated by x-ray sixteen years ago. If she had cancer at that time, as the record suggests, she would not be alive and well sixteen years later, either with or without x-ray treatment. So that I doubt very much if she had cancer sixteen years before she came in. For the same reason, I also doubt very much if she had lymphoma at that time, although some tumors of the lymphoma group do survive for relatively long periods. Furthermore, I do not understand why x-ray treatments given sixteen years ago afforded relief from her dizzy spells, palpitation and sensations of fainting. Nor is it easy to explain the ten-year period of freedom from symptoms before there was a recurrence, once again with relief after x-ray treatment. I am forced to conclude that the dizziness and related symptoms bore no relation to the mediastinal tumor, and that x-ray treatment of the chest to relieve them was irrational.

It seems to me that in the differential diagnosis we must first exclude a chest-wall tumor. The x-ray films do that satisfactorily. The physical signs are those of tumor. The films suggest that it is a solid tumor, and one can fairly well exclude tumor of the lung, because of the lack of symptoms and because of the x-ray findings. We therefore have to assume, if we exclude these two sources, that this tumor arose primarily from the mediastinum, although it has pushed into the left chest rather far. The heart and other mediastinal structures have been pushed to the right. The statement is made, and it seems apparent from the x-ray films, that the tumor was in the anterior part of the chest, although it has grown posteriorly to some extent. I assume it did not arise in the posterior part. Solid or cystic tumors arising in this region are relatively few, as you know. We have seen tumors — not of this size, in my experience — arising from the thymus. Last summer, we had a dermoid cyst in the mediastinum arising from thymus remnants, but that was no bigger than a baseball. This is too big to be a thyroid tumor. I suppose lymphoma might be mentioned, but it does not look to me like lymphoma, in spite of the long history and the relief after x-ray therapy. It could be a dermoid cyst. It shows no calcification, but that is not necessary by any means. If it had arisen from the posterior mediastinum, we should have an excuse for mentioning neurofibroma, since tumors of that group commonly occur in the posterior mediastinum. At any rate, although I cannot make a definite diagnosis of what the tumor is, I should say it was a solid or cystic tumor, and that the patient ought to be operated on.

Dr. Tracy B. Mallory: Dr. Bland, you saw this patient in relation to the attacks of dizziness and fainting.

Dr. Edward F. Bland: For fifteen years, she had had paroxysmal attacks of rapid heart action, which I assume were responsible. On examination, I did not find anything wrong with her heart. Later, she had an attack of tachycardia that lasted fifteen minutes, but when I saw her, her heart action was again normal, the blood pressure was all right, and her condition was good. I ordered 3 gr. quinidine, three times a day, as a prophylactic measure.

Dr. Ralph Adams: As Dr. Churchill's associate, I saw this patient and believed preoperatively that she had a dermoid cyst. I also thought of teratoma.

Dr. Edward D. Churchill: We had the advantage of seeing an x-ray film taken five years previously, which was apparently identical with the ones you see here. Several needle aspirations had been attempted, but her physicians never obtained anything but blood, so that we did not try thoracentesis. We were faced with a rather difficult situation in regard to indications for operation because this woman was getting along quite well except for her attacks of dizziness. It was known that the mass had been present for at least five years, and she was fifty-three years of age. She had been prepared for operation in another city, but a heart attack led to cancellation of the program. Our line of reasoning was a good deal the same as that in a case of dermoid cyst presented here a few weeks ago. That is, this patient was reaching an age at which she might be expected to have more frequent symptoms related to her heart, and for the rest of her life her medical advisers would face the dilemma whether to take the tumor out or to let her carry on and accept any cardiac embarrassment that the tumor might be causing. Also, it was impossible to dissociate symptoms that might arise from intrinsic heart impairment and heart action disturbed by the presence of the huge tumor. However, we assured her physician that we reserved the privilege of making a dignified retreat if we thought the removal of the tumor would in itself be too hazardous. In other words, we did not want to assume a foolish risk with an eye on the trophy because of the relatively comfortable life that this woman was able to lead. When we did open the chest, it was found that the tumor was readily resectable. She made an uneventful recovery. I do not believe we made a definite preoperative

diagnosis — any more definite than that made by Dr. Sweet.

DR. ADAMS: "Excision of mediastinal tumor" is written on the operative sheet. As we discussed it preoperatively, I believe we leaned toward teratoma.

DR. MALLORY: Can you describe the location of the mass at operation?

DR. CHURCHILL: It seemed to be from the anterior mediastinum. It filled the whole hemithorax.

DR. MALLORY: Could it have arisen from the sympathetic chain?

DR. CHURCHILL: No; it was too far anterior. The phrenic nerve was displaced backward by the tumor.

CLINICAL DIAGNOSIS

Mediastinal tumor.

DR. SWEET'S DIAGNOSIS

Benign tumor of the anterior mediastinum (possibly dermoid cyst).

ANATOMICAL DIAGNOSIS

Perineurial fibroma.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The tumor, as is of course obvious from the x-ray films, was an extremely large one. Its whole central portion was necrotic — a mass of dead tumor tissue and hemorrhage, around which lay a rim of viable tumor of varying thickness. There were some spots that looked yellow in gross, and one area almost suggested the membranous lining of a cyst so that the question arose whether it might be a dermoid. On microscopic examination, however, it is quite obvious that it is a fibromatous tumor and equally obvious that it is of neurogenous origin; in fact, one might, I believe, classify it as schwannoma, although such tumors do not usually grow to this size or show necrosis in the center. The outlook I think is good. It is unlikely that there will be a recurrence.

DR. CHURCHILL: It is not a malignant tumor?

DR. MALLORY: I should say not. Our original impression, I confess, was fibrosarcoma.

DR. CHURCHILL: Have you taken several sections in varying parts to be sure that there was only one germ layer involved?

DR. MALLORY: We have gone back to the gross specimen and picked more suspicious areas from that point of view, and found no other form of tissue. The tumor is obviously of nerve-sheath origin.

DR. HELEN S. PITTMAN: Then it could not have responded to x-ray therapy?

DR. MALLORY: It seems improbable.

A PHYSICIAN: Where did it arise?

DR. MALLORY: There are sympathetic nerves everywhere, and it did not have to arise from a grossly namable one.

DR. BLAND: Have the attacks of rapid heart action been less frequent since the operation?

DR. CHURCHILL: I have not had a follow-up report yet.

DR. BLAND: In one attack during her hospital stay, we were able to get an electrocardiogram, which showed that her rapid heart action was due to auricular flutter. Several of the recent cases of flutter we have recorded have been in patients who have had something seriously wrong in their chests and have been operated on.

DR. CHURCHILL: It comes as a postoperative complication not infrequently.

DR. ADAMS: Of the four cases of flutter that Dr. Bland and I have been thinking of, two occurred in association with anterior mediastinal tumors, one in a thoracoplasty in which the apical adhesions had required considerable dissection anteriorly, and the fourth in a case of lobectomy for bronchiectasis.

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WARTIME TRANSFUSION THERAPY

Even war has its mitigations. In the present carnage, it is probable that much will be learned regarding surgical shock and its treatment by the injection of blood or one of its components.

Ten or fifteen years ago, certain Russian investigators drew blood from healthy cadavers; this was citrated, stored and given to patients, with good results. The possible value of this maneuver on the battlefield was obvious. Stored citrated blood obtained from healthy living persons was also used with success; the war in Spain proved that the method could be adapted to use on a large scale. During this period, the British medical journals began to publish numerous articles dealing with blood banks, and long before the present war began, the British medical profession had prepared for trouble by equipping each section of London with a decentralized blood bank and a supply of volunteer donors. In this country, the first successful blood bank was organized a few years ago at the Cook County Hospital in Chicago, and since then, a number have been in successful operation.

For a hospital of at least two hundred beds in which there is a fairly large volume of surgery and obstetrics, the blood bank is very useful, particularly to the overworked intern. The bank, nevertheless, has its limitations. Blood gradually deteriorates even when stored at 2 to 4°C.: the immune bodies and prothrombin diminish considerably, the leukocytes and platelets disappear quickly, and the red cells become spheroidal and thus readily broken up in the circulation. For these reasons, fresh blood is distinctly preferable in the treatment of blood dyscrasias, chronic anemia and those acute infections in which the antibody or prothrombin content of the injected blood may be of some importance. Furthermore, transfusion reactions appear to be commoner with bank blood, and there is still the necessity for typing and cross-matching.

During the last year or two, the value of serum or plasma transfusions has been clearly demonstrated. For surgical shock, in which the symptoms are chiefly due to the loss of plasma from the circulating blood, it is of the utmost importance to inject intravenously a substance that remains in the circulation. The red blood cells are not needed, unless there has been serious hemorrhage, and blood serum or plasma is the ideal material. Furthermore, the use of pooled serum or plasma has several advantages. In the first place, it can be transported easily and stored for long periods — practically indefinitely in dried form. Secondly, since pooled samples lose their blood-group characteristics, it can be given quickly and indiscriminately, without wasting time for typing and cross-matching. Thirdly, it can be injected, if desired, in two or three times its normal concentration. Appreciating these facts, the

British Red Cross appealed last summer to the American Red Cross for a supply of plasma, and up to February of this year, when plans had been perfected for obtaining the supply in England, the American Red Cross, in co-operation with the Blood Transfusion Betterment Association, collected and shipped approximately 15,000 pints of liquid plasma.

With the shipments to England ended, the American Red Cross, at the request of the Surgeons General of the United States Army and Navy, has now undertaken to provide a national reservoir of blood plasma for emergency use. It is being prepared in two forms: ordinary fluid plasma and dry, powdered (lyophilized) plasma, which is made ready for immediate use by the addition of sterile distilled water. Thus, thanks to the American Red Cross and affiliated agencies, the Army and Navy will have available quantities of plasma, ready for instant use.

For the treatment of anemia, leukopenia and thrombopenia and of infectious processes, fresh blood obtained directly from healthy donors is still preferable. For emergency use in surgical shock, even when accompanied by a moderate amount of hemorrhage, plasma is probably as useful as whole blood. Thus the importance of a bank for storage of whole blood will probably diminish as dried plasma becomes commercially available.

Blood in "tin cans"! Thus does science advance even as moral values reach low ebbs. The American Red Cross is to be congratulated for its sponsorship of still another humane project, which will certainly find its ultimate value in days of peace.

HANS BERGER

HANS BERGER,* one of the foremost neuropsychiatrists of our time, discoverer of the electrical waves of the human brain, died on July 7, in Jena, at the age of sixty-eight. His important contribution to medicine, when first reported in 1929, was considered by many as ludicrous. In the last ten years, however, it has been shown not only that his discovery was sound, but that, because the rhythmic, electrical discharge is altered in various normal and abnormal mental conditions, particularly in epilepsy, a new and highly significant technic, electroencephalography, had been made available for neurologic and psychiatric investigation.

To some of his contemporaries, this great achievement seemed like a stroke of luck, but viewed in terms of his earlier work and his life method it was the end result of a long and persistent search. From his days as a *Privatdozent* onward, he was a determined experimentalist. He proceeded on the assumption that the brain is a physicochemical machine, of which the chief product is behavior; and he was continually looking for what he called the physical concomitants of mental activity. His first studies were on the cerebral pulse, and he used its wave form and the interval between it and the apex beat to indicate the state of the cerebral vascular bed. Two of his early books, *The Intracranial Circulation* (1901) and *Organic Manifestations of Mental States* (1904–1907), contain reports of this work. His experiments on cerebral circulation were by no means impressive, but this was largely because no major changes in cerebral blood flow occur in association with the conditions he studied, namely, mental work, fright, sleep and states initiated by various types of sensory stimuli. These facts could not have been proved from deductive reasoning.

Berger next turned his attention to the study of the temperature of the brain, and again he failed to find important correlations. Despite these negative results, three books, entitled *Studies on the Temperature of the Brain* (1910), *Trauma and the Psychoses* (1915) and *Localization in the Cerebrum* (1927), revealed in his work a persistently physiologic point of view.

In 1924, at the age of fifty-one, when many determined experimenters weaken and lapse into speculation, Berger started his epoch-making work

*An exhibit of material depicting Berger's discovery is now on display in the rotunda of the Boston Medical Library through the kindness of Dr. Frederic A. Gibbs.

on the electrical activity of the brain. His search for electrical accompaniments of mental activity was, as a matter of fact, a return to a youthful line of investigation that he had started in 1902.

The significance of Berger's discovery was vaguely grasped by Adrian and Matthews, in England, in 1933, and the name, "Berger's rhythm," was given to the electrical discharge of the brain by the same authors in 1934. They, erroneously, thought that the waves originated in the occipital lobe and were identified with vision. By 1936, electroencephalography was firmly established in this country as a clinical and experimental technic, and much of the subsequent knowledge of the Berger phenomenon has originated in the United States.

Berger's discovery has become a cornerstone in the slowly growing structure of neurologic and psychiatric knowledge and affords a new basis for the dynamic approach to the study of brain function.

MEDICAL EPONYM

Jackson's Membrane

Jabez N. Jackson (1868–1935), of Kansas City, Missouri, read a paper before the Western Surgical Society at Minneapolis, Minnesota, in December, 1908, entitled "Membranous Pericolitis." This was printed with revisions and additions in *Surgery, Gynecology and Obstetrics* (**9**: 278–287, 1909).

> Wherever . . . we find any late manifestations of peritoneal disturbance about the colon we have been content to label it "adhesions," presume an antecedent acute appendicitis, and pass on. Some very striking . . . observations . . . have persuaded [the writer] that there is a most interesting pathological condition occurring about the right colon which can not thus readily be set aside. . . . The following description . . . is . . . from the report of Dr. Frank Hall, pathologist. . . . "From a point just at the hepatic flexure to three inches above the caput there spreads from the parietal margin over the external lateral margin to the internal longitudinal muscle band a thin vascular veil."
>
> Synchronously with our recognition of the distinct pathology and clinical identity of this condition, we had been impressed with the view that this pericolonic membrane by its mechanical interference with colonic peristalsis was possibly, if not probably, responsible for the chain of symptoms which were manifest when it was found present.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Attempted Forceps Delivery and Cesarean Section, Followed by Death

A forty-year-old para IV entered the hospital at term, after being in labor for twenty-four hours at home. She was under ether when admitted.

The prenatal care during this pregnancy had been inadequate. The past history was irrelevant. The three previous pregnancies had terminated in normal deliveries, none of the babies weighing more than 6 pounds.

Prior to admission, the patient's family physician had unsuccessfully attempted forceps delivery, and the patient arrived at the hospital with the cord prolapsed. According to the admission note, the cervix was dilated to admit two fingers, the head was high, and a nonpulsating cord presented. The pulse rate was not recorded. A classic cesarean section was immediately performed, and an 8-pound, 5-ounce, stillborn baby was delivered. A drain was placed in the pelvis. During the first two weeks of convalescence, there was some febrile reaction, but no evidence of a generalized peritonitis. On the fourteenth day, the wound broke down, and evisceration of the bowels occurred. The bowels were replaced, the wound was resutured, and the patient was transfused. She died nineteen days after operation, the death certificate stating that she died of bronchopneumonia.

Comment. From beginning to end, this case represents poor obstetrics. The apparent size of the child, particularly in view of the fact that the three other babies were small, and the height of the head should have stimulated inquiry and possibly x-ray study. This patient undoubtedly had some form of contracted pelvis. When she entered the hospital, the cervix was said to have been only slightly dilated. This probably meant that the cervix had shut down after the attempt at delivery had failed, because it is not imaginable that anyone would attempt forceps delivery with such a dilatation of the cervix.

There were two ways of treating this patient after she arrived in the hospital with the cord prolapsed, the baby dead and the uterus probably infected. One would have been an extraperitoneal section of the Waters type, accompanied by transfusion. If this had seemed to be contraindicated, cesarean section with hysterectomy would have been the operation of choice. This is a death resulting from intraperitoneal cesarean section, which was contraindicated from the outset.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section. Letters should be addressed to Dr. Raymond S. Titus, *Secretary*, 330 Dartmouth Street, Boston.